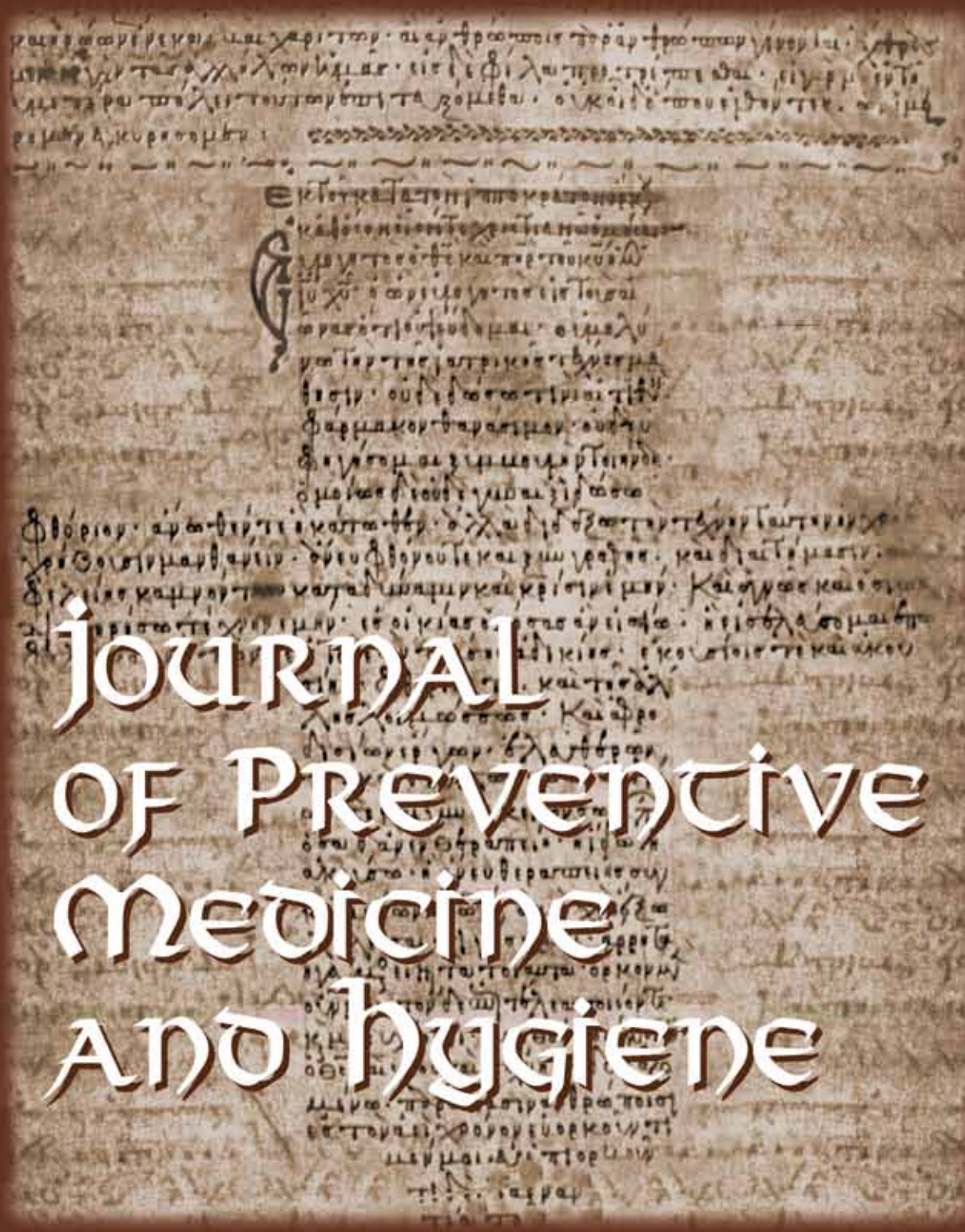


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# JOURNAL OF PREVENTIVE MEDICINE AND HYGIENE

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## REVIEW

# Operating theatre quality and prevention of surgical site infections

A.M. SPAGNOLO, G. OTTRIA, D. AMICIZIA, F. PERDELLI, M.L. CRISTINA  
Department of Health Sciences, University of Genoa, Italy

## Key words

Operating theatre • Surgical site infections • Quality

## Summary

*Surgical site infections (SSI) account for 14% to 17% of all hospital-acquired infections and 38% of nosocomial infections in surgical patients. SSI remain a substantial cause of morbidity and death, possibly because of the larger numbers of elderly surgical patients or those with a variety of chronic and immunocompromising conditions, and emergence of antibiotic-resistant microorganisms.*

*Factors causing surgical site infection are multifarious. Several studies have identified the main patient-related (endogenous risk factors) and procedure-related (external risk factors) factors that influence the risk of SSI. The rate of surgical wound infections is strongly influenced by operating theatre quality, too. A safe and salubrious operating theatre is an environment in which all sources of pollution and any micro-environmental alterations are*

*kept strictly under control. This can be achieved only through careful planning, maintenance and periodic checks, as well as proper ongoing training for staff.*

*Many international scientific societies have produced guidelines regarding the environmental features of operating theatres (positive pressure, exchanges of filtered air per hour, air-conditioning systems with HEPA filters, etc.) and issued recommendations on healthcare-associated infection, including SSI, concerning surveillance methods, intervention to actively prevent SSI and approaches to monitoring the implementation of such strategies. Therefore, the prevention of SSI requires a multidisciplinary approach and the commitment of all concerned, including that of those who are responsible for the design, layout and functioning of operating theatres.*

## Introduction

Surgical care is an integral part of health care throughout the world, with an estimated 234 million operations performed annually [1]. However, surgical care is also associated with a considerable risk of complications and death.

A study on the incidence and nature of in-hospital adverse events has shown that 1 in every 150 patients admitted to a hospital dies as a consequence of an adverse event and that almost two thirds of in-hospital events are associated with surgical care [2].

Surgical site infections (SSIs) remain one of the most common causes of serious surgical complications [3]; they account for 14% to 17% of all hospital-acquired infections and 38% of nosocomial infections in surgical patients [4, 5].

Each SSI is associated with approximately 7-10 additional postoperative hospital days and patients with an SSI have a 2-11 times higher risk of death, compared with operative patients without an SSI [6, 7].

In a nested-cohort study carried out in a 750-bed tertiary-care hospital in North Carolina, US, elderly patients with SSIs due to *Staphylococcus aureus* were at increased risk of mortality (odds ratio – OR: 5.4), increased post-operative hospital days (2.5-fold increase)

and increased hospital charges (2.0-fold increase) compared with controls (uninfected elderly patients) [8].

## Surgical site infections

Surgical site infections (SSIs) are defined as infections occurring up to 30 days after surgery (or up to one year after surgery in patients receiving implants) and affecting either the incision or deep tissue at the operation site [9].

Particularly, SSI can sometimes be superficial infections involving the skin only. Other surgical site infections are more serious and can involve tissues under the skin, organs, or implanted material.

There are 3 different types of surgical site infection defined by the Centers for Disease Control and Prevention (CDC): *superficial* infections, *deep incisional* infections and infections involving *organs or body spaces* (Tab. I) [10].

Severe SSIs in deep incisions or organ spaces account for almost half of all SSIs [11].

The degree of surgical site contamination at the time of surgery influences the probability of surgical site infection.

According to the presence and degree of contamination, wounds can be classified as: “clean wounds”, “clean-

Tab. I. Surgical site infection classification.

<p><b>Superficial Incisional SSI</b></p> <p>Infection occurs within 30 days after the operation <i>and</i> infection involves only skin or subcutaneous tissue of the incision <i>and</i> at least <i>one</i> of the following:</p> <ol style="list-style-type: none"> <li>1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.</li> <li>2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.</li> <li>3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, <i>unless</i> incision is culture-negative.</li> <li>4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.</li> </ol> <p>Do <i>not</i> report the following conditions as SSI:</p> <ol style="list-style-type: none"> <li>1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).</li> <li>2. Infection of an episiotomy or newborn circumcision site.</li> <li>3. Infected burn wound.</li> <li>4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).</li> </ol> <p><i>Note:</i> Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.</p>
<p><b>Deep Incisional SSI</b></p> <p>Infection occurs within 30 days after the operation if no implant* is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:</p> <ol style="list-style-type: none"> <li>1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.</li> <li>2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (&gt; 38°C), localized pain, or tenderness, unless site is culture-negative.</li> <li>3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.</li> <li>4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.</li> </ol> <p><i>Notes:</i></p> <ol style="list-style-type: none"> <li>1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.</li> <li>2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.</li> </ol>
<p><b>Organ/Space SSI</b></p> <p>Infection occurs within 30 days after the operation if no implant* is left in place or within 1 year if implant is in place and the infection appears to be related to the operation <i>and</i> infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation <i>and</i> at least <i>one</i> of the following:</p> <ol style="list-style-type: none"> <li>1. Purulent drainage from a drain that is placed through a stab wound** into the organ/space.</li> <li>2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.</li> <li>3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.</li> <li>4. Diagnosis of an organ/space SSI by a surgeon or attending physician</li> </ol>

\* National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery; \*\* If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth. Reproduced with permission from Horan TC [10].

contaminated wounds”, “contaminated wounds”, “dirty or infected wounds” [10, 12, 13].

Infection rates in the four surgical classifications have been published in many studies. Before antibiotic prophylaxis was routinely used, the rates were about 1-2% for clean wounds, 6-9% for clean-contaminated wounds, 13-20% for contaminated wounds and 40% for dirty wounds. As the level of bacterial burden is the most significant risk factor for SSIs, the use of prophylactic antibiotics has markedly reduced this risk [14], particularly with surgical procedures at high risk of infection, such as those involving the gastrointestinal tract [15].

However, SSI remain a substantial cause of morbidity and death, possibly because of the larger numbers of elderly surgical patients or those with a variety of chronic and immunocompromising conditions, greater use of prosthetic implants and organ transplantation and emergence of antibiotic-resistant micro-organisms [16]. Over the last decade, there has been little variation in the in-

cidence and distribution of the pathogens isolated from infections [17]; however, an important change in the microbiology of SSIs has been the increasing involvement of microorganisms that are resistant to antibiotic treatment.

Indeed, the number of SSIs caused by methicillin-resistant *S. aureus* (MRSA) has increased dramatically [4].

## Microbiology

The pathogens isolated from infections differ, primarily depending on the type of surgical procedure. In clean surgical procedures, in which the gastrointestinal, gynecologic, and respiratory tracts have not been entered, *Staphylococcus aureus* from the patient’s skin flora is the usual cause of infection. When mucous membranes or skin is incised, the exposed tissues are at risk of contamination by *endogenous* flora [10].



Approximately 20 to 30% of surgical-site infections are caused by *S. aureus*, and over half of these arise from the endogenous flora [18]. Anderson et al. described a total of 1,010 SSIs occurred after 89,302 procedures in 26 hospitals; *S. aureus* was the organism most commonly isolated, recovered from 331 (37%) of SSIs. Of the 331 *S. aureus* SSIs, 175 (53%) were caused by MRSA, making MRSA the single most commonly isolated pathogen [19]. Furthermore, recent studies have shown that reduced susceptibility to vancomycin and other glycopeptides, is emerging in different MRSA clones all over the world [20, 21].

In other categories of surgical procedures, including clean-contaminated, contaminated, and dirty, the polymicrobial aerobic and anaerobic flora closely resembling the normal endogenous microflora of the surgically resected organ are the most frequently isolated pathogens [22].

Occasionally, the pathogenic microorganisms are acquired from an *exogenous* source, such as the operating theatre environment, surgical personnel [23] and all tools, instruments, and materials brought to the sterile field during an operation.

The most commonly isolated organisms are *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp. and *Escherichia coli* [9, 24]. Giacometti et al. [25] studied 676 surgery patients with signs and symptoms indicative of wound infections, who presented over the course of 6 years. Bacterial pathogens were isolated from 614 individuals. A high preponderance of aerobic bacteria was observed. Among the common pathogens were *Staphylococcus aureus* (28.2%), *Pseudomonas aeruginosa* (25.2%), *Escherichia coli* (7.8%), *Staphylococcus epidermidis* (7.1%), and *Enterococcus faecalis* (5.6%).

## Risk factors

The risk of developing SSI varies greatly according to the nature of the operative procedure and the specific clinical characteristics of the patient undergoing that procedure [23].

Several studies have identified the main patient-related (endogenous) and procedure-related (external) factors that influence the risk of SSI [9]. Potential patient-related factors include malnutrition, older age, coexistent infection, and diabetes. A review of Dominioni et al. [26] showed that in the hierarchy of patient-related risk factors, serum albumin concentration and advanced age rank at the top of the list. Apart from endogenous factors, the role of external risk factors in the pathogenesis of SSI is well recognized [10].

External risk factors include the type and duration of operation, surgeon's skill, the quality of preoperative skin preparation, adequacy and timing of antimicrobial prophylaxis, insertion of foreign material or implants, inadequate sterilisation of surgical instruments [10, 27]. The rate of surgical wound infections is strongly influenced by operating theatre quality, too. [15].

## Operating theatre quality

A safe and salubrious operating theatre is an environment in which all sources of pollution and any micro-environmental alterations are kept strictly under control. This can be achieved only through careful planning, maintenance and periodic checks, as well as proper ongoing training for staff [28].

Indeed, an operating theatre is an extraordinarily complex system in which numerous risk factors are present, including not only the features of the structure and its fixtures, but also the management and behaviour of healthcare workers.

## Structural features

The structural features of the operating unit can influence not only the efficacy of the treatment provided, but also the outcome of the patient in terms of the prevention of surgical infections.

The design of the operating unit is complex and requires that different areas be correctly integrated. In addition to keeping clean and dirty areas separate, it is important to ensure that patient flow, from arrival to discharge, is orderly and logical.

Specific rooms should be designated for performing surgical procedures and for processing instruments and other items. It is important to control traffic and activities in these areas since the number of people and the amount of activity influence the number of microorganisms that are present and therefore influence the risk of infection. The operating unit should be arranged in progressively less contaminated areas, from the reception area to the operating theatres. Moreover, organisational/functional and/or structural intervention must be implemented in order to ensure that "dirty" and "clean" pathways be kept separate. The size of storage areas for dirty material, clean material, supplies, instruments, equipment and drugs must be determined in accordance with the type and volume of activity of the operating unit [29].

Moreover, in designing an operating unit, the choice of surface finishes, as well as structural features, is of great importance; surfaces should be easy to clean in order to facilitate infection control. Design, layouts, fittings, furnishings, floor coverings and finishes will have a significant impact on the cleaning of the unit. Ledges, corners and all other surfaces that are difficult to clean should be minimized.

The surfaces of floors should be impervious to moisture, easily cleaned, stain resistant, comfortable for long periods of standing and suitable for wheeled traffic. In the operating theatres the colour should be such that small items can easily be found, if dropped [30].

The surfaces delimiting the areas inside the operating unit, including those hidden from view (e.g. ceiling panels, rear panels of built-in fittings, etc) should also be smooth and easy to clean and should be compatible with the use of chemical and physical cleaning agents, as well as being waterproof, fireproof and resistant to

knocks. Window frames should be designed in such a way that their surfaces are easy to clean and do not collect dust [29].

## Ventilation

During surgical procedures, dust particles, textile fibers, skin scales, and respiratory aerosols loaded with viable microorganisms are released from the surgical team and the surrounding into the air of the operating theatre. Bacteria settling on surgical instruments or entering directly into the surgical site may result in surgical site infection (SSI) [31].

Therefore, maintaining a high quality of the air in the operating theatre is essential to controlling the risk of surgical infections. To reduce the morbidity and healthcare costs associated with these infections, airborne bacteria and other sources of contamination must be minimised. In this regard, a fundamental role is played by the contamination-controlled airflow system (heating, ventilation, air-conditioning system: HVAC). Indeed, in addition to maintaining temperature and humidity at optimal levels, this system provides ventilation that is able to keep the concentrations of gaseous pollutants, particulates and airborne microbes below predetermined levels. HVAC systems perform multiple functions simultaneously, including controlling three known central variables in the airborne transmission of infectious particles: temperature, relative humidity, and air currents.

Therefore, HVAC systems are intended to provide for the health, comfort, and safety of occupants by maintaining thermal and air quality conditions that are acceptable to the occupants [32].

In the operating theatre, the specific features of the airflow system which enable SSIs to be contained are ventilation (dilution), air distribution, room pressurization (infiltration barrier) and filtration (contaminant removal) [33].

The air in operating theatres should be kept at a higher pressure than in corridors and adjacent areas. This positive pressure prevents the flow of air from less sterile areas into more sterile ones [18].

With regard to ventilation, various international scientific organisations recommend a minimum of 15 air exchanges per hour. Specifically, the “Guidelines for environmental infection control in health-care facilities” issued by the CDC [34] recommend a minimum of about 15 exchanges of filtered air per hour, three (20%) of which must be fresh air. The 2008 edition of ANSI/ASHRAE/ASHE Standard 170 (“Ventilation of Health-care Facilities”) [35], recommends a minimum of 20 total air exchanges per hour and a minimum of 4 exchanges of outdoor air per hour in operating theatres. The main types of airflow systems are: turbulent-flow, unidirectional-flow and mixed-flow. Turbulent flow directly involves the whole environment, the concentration of airborne contaminants being controlled by means of dilution. This type of system increases the effectiveness of air exchange and distribution. However, it has the dis-

advantage of speeding up microbial dispersion [33]. In several countries, this type of airflow is generally considered adequate for operating theatres in which general surgery or similar operations are performed [29].

In unidirectional-flow systems (“laminar airflow or LAF”), the air travels in parallel lines and contaminants are carried away at the same velocity as the airflow. Low-velocity unidirectional flow tends to minimize the spread of airborne contaminants and direct them towards the exhaust outlets. This system, as opposed to turbulent flow, allows airborne particles to pass the operating area and prevents them from landing in the wound area [33]. Unidirectional airflow is designed to move particle-free air (called “ultraclean air”) over the aseptic operating field at a uniform velocity (0.3 to 0.5  $\mu\text{m}/\text{sec}$ ), sweeping away particles in its path [18].

From a purely technical standpoint, systems that provide laminar flow regimes constitute the best option for an operating theatre, in terms of contamination control, as they result in the smallest percentage of particles impacting the surgical site.

The reason for this is that such systems supply a controlled, constant column of air to the surgical site area; this is effective in sweeping contaminants from the surgical site area, where they might otherwise be deposited [36].

Laminar airflow through HEPA filters, which display 99.97% efficiency in removing airborne particles of 0.3  $\mu\text{m}$  and above, can be supplied to the operating area by ceiling-mounted (vertical flow) or wall-mounted (horizontal flow) units. It has been suggested [37, 38] that improper positioning of personnel in operating theatres with a horizontal and vertical laminar airflow may increase the risk of infection.

In the so-called mixed-flow system, unidirectional airflow regimes are only used to protect critical zones (e.g. the area surrounding the operating field) [29].

Most operating theatres have conventional ventilation and laminar air-flow systems with HEPA filters are generally used for orthopaedic and other implant surgery [27].

Charnley [39] evaluated 5,800 surgical operations; he showed that intraoperative contamination was a major threat to the success of total joint replacements, and revealed that the rate of SSI fell dramatically from 7 to 0.5% when unidirectional airflow regimes with a high number of hourly air exchanges were adopted and surgical staff wore special suits that covered the whole body. Subsequently, other studies [40-42] have shown that fewer infections arise when orthopaedic surgery is performed in operating theatres with ultra-clean air facilities.

Currently, there is no complete consensus in the scientific community with regard to the need to use unidirectional airflows in prosthetic orthopaedic surgery, since no prospective studies comparing air quality with SSI rates are available.

In theory, preventing contamination by flowing particle-free air unidirectionally over the surgical site can potentially reduce the risk of SSI. Although this method is

biologically plausible, and some previous studies have supported this concept, a meta-analysis encompassing 26 studies could not ultimately confirm the role of LAF in surgery, and some recent studies have even indicated an increase in SSI after hip prosthesis with procedures performed under LAF [43, 31].

In view of these contradictory results – but, more importantly, in view of worldwide increases in health care costs and increasing difficulties in financing and providing all modern medical advances – it is understandable that the question arises regarding the actual need for LAF ventilation in operating theatres to prevent SSIs [31].

## Water

The water distribution system in hospitals may constitute a source of healthcare-associated infections caused by opportunistic pathogens such as: *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Acinetobacter* spp, fungi, etc. Taps are common sources of *P. aeruginosa* and other Gram-negative bacteria and have even been linked to infections in multiple hospital settings [44].

Other hospital equipment, such as water-cooled high-speed drills in dental surgeries [45] is of particular concern for both inhalation of aerosols and infection of wounds. Indeed, aerosols and droplets produced by dental instruments connected to dental unit waterlines during dental care may contain microorganisms that can be opportunistic pathogens for patients and dentists [46, 47]. Only a small number of published studies deal with cases of infections associated with dental caries. But the obvious concern is that large numbers of potentially pathogenic microorganisms may be swallowed, inhaled or alternatively inoculated into oral wounds during dental treatment with a potential for both colonization and infection [48].

Immunocompromised patients are particularly susceptible to infection by waterborne microorganisms, which can cause bacteraemia, pneumopathy, meningitis, urinary tract infections and surgical site infections [49-51]. Apart from water used in dental surgery, another area of environmental control in operating theatres is the bacteriological quality of water used for surgical handscrubs for which there are no standardized limits at present.

Surgical hand antisepsis with medicated soap requires clean water to rinse the hands after application of the medicated soap.

Indeed, despite the use of surgical gloves, the transmission of microorganisms from the hands of the surgeon to the patient may occur due to microperforations that happen at an average of 18% (5-82%) at the end of the surgery. After two hours of surgery, 35% of all gloves demonstrate puncture, thus allowing water (hence also body fluids) to penetrate the gloves without using pressure. In over 80% of cases, such perforations are not perceived by surgeons, and microperforations can double the risks of infection in the surgical site, thus turning the prior preparation of the hands into a crucial step [52]. A

recent trial demonstrated that punctured gloves double the risk of SSIs. Double gloving decreases the risk of puncture during surgery, but punctures are still observed in 4% of cases after the procedure. Several reported out-breaks have been traced to contaminated hands from the surgical team despite wearing sterile gloves [53].

However, infections clearly linked to contaminated hands of surgeons after surgical hand scrub with contaminated water have not yet been documented.

In countries lacking continuous monitoring of drinking-water and improper tap maintenance, recontamination may be a real risk even after correct surgical hand scrub.

## Procedural and behavioural factors

Other aspects of the complex strategy to minimize infection risk during surgical operations are procedural and behavioural factors that can also have a negative impact on the surgical outcome.

In general, the strategy for reducing intra-operative contamination involves a systemic and behavioural approach. As already seen, a systemic approach consists of improving the airflow system. A behavioural approach aims to reduce the number of airborne particles in the operating theatre through disciplinary measures. Simple and cheap measures include limiting the number of personnel in the operating theatre and restricting the movements of personnel in the operating theatre to a minimum, as it has been shown that increased activity facilitates the dispersion of bacteria [54].

In addition to the number and movements of personnel in the operating theatre, adverse surgical events may be due to poor communication, bad operative technique, malfunctioning or improperly used equipment, and cognitive errors due to stress or inattention, all compounded by resource and organizational problems. Communication in the operating suite is often poor and may contribute to adverse outcomes [55].

Knobben et al. [56] found that, in patients undergoing orthopaedic implant surgery, adopting a range of measures in the operating theatre had a significantly positive effect on outcomes during the postoperative period. In that study, the measures adopted involved limiting needless activity, correct use of plenum (area of laminar flow), work-up in the preparation room rather than in the operating theatre, and the wearing of proper attire. These Authors observed that the combination of systemic and behavioural measures in the operating theatre led to a reduction in the incidence of intra-operative bacterial contamination and, consequently, of prolonged wound discharge and superficial surgical site infection. Moreover, after one-year follow-up, fewer deep periprosthetic infections were recorded. While it is difficult to determine the relative influence of each individual measure on the final result, the combination of all these parameters evidently creates the most effective weapon against infections. To maintain low bacterial counts, both the airflow system and behaviour have to be monitored by an in-

fection committee. Both positive and negative feedback helps to maintain the reduction in bacterial dispersal. Finally, it is important to emphasize that all personnel working in operating theatres, including surgeons, operating theatre assistants, anaesthesiologists and cleaning personnel, must follow hygiene protocols very strictly. In 2008, the World Health Organization (WHO) published guidelines identifying multiple recommended practices (including a "Surgical Safety Checklist") to ensure the safety of surgical patients worldwide [3]. The Surgical Safety Checklist comprises 19 items in three parts to be completed in a total of 3 min at key points in surgical procedures. The items include measures such as confirming patients' names and procedures, introducing theatre staff to patients, and ensuring that prophylactic antibiotics to prevent surgical-site infection are used appropriately [57]. Basically, the checklist includes three moments of formalized briefings and safety checks: a 'sign in' before induction of anaesthesia, a 'time out' before skin incision and a 'sign out' before the patient leaves the operating room.

Haynes and co-Authors [58] found that introducing the WHO Surgical Safety Checklist into operating theatres in eight diverse hospitals was associated with marked improvements in surgical outcomes. Postoperative complication rates fell by 36% on average, and death rates were reduced to a similar degree. The overall rates of surgical-site infection and unplanned reoperation also declined significantly ( $p < 0.001$  and  $p = 0.047$ , respec-

tively). In order to apply the checklist, surgical staff had to pause before the induction of anaesthesia, before skin incision and before the patient left the operating theatre; in previous studies, these team practices had already been associated with improved safety processes and attitudes and with a marked reduction in rates of complications and death. Checklist implementation encouraged the administration of antibiotics in the operating theatre rather than in the preoperative wards. The checklist provided additional oral confirmation of appropriate antibiotic use, increasing the adherence rate from 56 to 83%. This intervention alone has been shown to reduce the rate of surgical-site infection by 33 to 88% [59, 60].

In conclusion, surgical site infection rates can be improved by acting upon various factors, from the surgical environment itself to procedural aspects and staff behaviour. Moreover, surveillance of SSIs is a well-established, well documented approach to lower the incidence of SSIs. Many hospitals still do not follow this recommendation despite its effectiveness.

The Centers for Disease Control and Prevention guidelines for the prevention of SSIs emphasise the importance of good patient preparation, aseptic practice, and attention to surgical technique; antimicrobial prophylaxis is also indicated in specific circumstances.

Therefore, the prevention of SSI requires a multidisciplinary approach and the commitment of all concerned, including that of those who are responsible for the design, layout and functioning of operating theatres.

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## REVIEW

# Biphosphonates-associated osteonecrosis of the jaw: the role of gene-environment interaction

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## Key words

Jaw osteonecrosis • Biphosphonate • Single nucleotide polymorphisms

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## summary

*Biphosphonate (BPN) are widely used in clinics to treat metastatic cancer and osteoporosis thus representing a problem not only for patients but also for workers involved in their preparation and administration. A similar exposure occurred years ago in match-making workers undergoing bone alterations similar to those consequent to BPN exposure. Osteonecrosis of the jaw (ONJ) is a main adverse effect related to BPN administration, which is performed in millions of patients worldwide for osteoporosis and cancer therapy, thus representing an emerging problem in public health. In susceptible patients, BPN induce severe, progressive, and irreversible degeneration of facial bones, resulting in avascular ONJ often triggered by dental surgery. BPN induced*

*ONJ occurs in subjects depending on lifestyle factors of both environmental and endogenous origins. Exogenous risk factors include cigarette smoke, alcohol consumption, bacterial infections, and cyclosporine therapy. Endogenous risk factors include systemic diseases such as diabetes or hypertension and adverse polymorphisms of genes involved in metabolism (CYPs, MTHFR), thrombosis (Factor V, Prothrombin), and detoxification (MDR). Available molecular findings provide evidence that ONJ is related to risk-factors associated with environmental mutagenesis and gene-environment interactions. This issues may be useful to identify susceptible subjects by molecular analyses in order to prevent ONJ occurrence.*

## Introduction

Biphosphonate (BPN) are widely used in clinics to treat metastatic cancer and osteoporosis thus representing a problem not only for patients but also for workers involved in their preparation and administration. A similar exposure occurred years ago in match-making workers undergoing bone alterations similar to those consequent to BPN exposure. Osteonecrosis of the jaw (ONJ) is a main adverse effect related to BPN administration, which is performed in millions of patients worldwide for osteoporosis and cancer therapy [1].

In susceptible patients, BPN induce severe, progressive, and irreversible degeneration of facial bones, resulting in avascular ONJ triggered by dental surgery. BPN induced ONJ occurs in subjects undergoing exposure to DNA-damaging agents as resulting from chemo and radiotherapy of neoplastic diseases or lifestyle factors. Thus, multiple risk factors of both environmental and endogenous origin contribute to BPN-related ONJ.

BPNs association with ONJ was first described in patients with cancer such as multiple myeloma, breast cancer, and prostate cancer treated with intravenous BPN [2]. Nowadays BPN treatment is considered the main risk factor for the development of ONJ. This disease mainly appears in patients receiving intravenous BPNs for the treatment of cancer or oral BPNs for the treatment of osteoporosis [1]. Numerous risk factors of

ONJ have been described mainly dealing with the interaction between genetic and environmental factors. Gene-environment interactions underline how genetic and environmental factors jointly influence the risk of developing a disease. Recent studies shed light on a substantial genetic component in the etiology of dentistry disease, paralleled by the established effect of environmental factors such as smoking, alcohol, radiation, and drugs [3].

The purpose of this review is to analyze how environmental factors interact with genetic assets to contribute to the development of ONJ. This knowledge may be useful to identify individuals at risk for developing this pathology.

## Exogenous risk factors and oral osteonecrosis

### BIPHOSPHONATES AND OSTEONECROSIS OF THE JAW

The structure of bisphosphonates (BPNs) is similar to that of endogenous pyrophosphate, a natural potent inhibitor of osteoclast-mediated bone resorption [4]. Consequently, BPNs have the same properties of inorganic pyrophosphates, but are resistant to hydrolysis, as well as pyrophosphatase enzymes. Etidronate, precursor of pamidronate, is the base molecule of the more potent

**Tab. I.** Biphosphonates approved for clinical use by United States of America Food and Drugs Administration (FDA). N-BPs = Nitrogen-containing Biphosphonates.

Drug compound	N-BPNs	Medical uses	Administration route
Alendronate	Yes	Osteoporosis, Paget's disease	Oral
Clodronate	No	Hypercalcemia of malignancy	IV/Oral
Etidronate	No	Paget's disease, hypercalcemia of malignancy, osteoporosis	Oral
Ibandronate	Yes	Osteoporosis, Paget's disease	Oral/IV
Pamidronate	Yes	Hypercalcemia of malignancy, Paget's disease, osteoporosis	IV
Risedronate	Yes	Osteoporosis, Paget's disease	Oral
Tiludronate	No	Paget's disease	Oral
Zoledronate	Yes	Hypercalcemia of malignancy	IV

second-generation drugs. The third generation structure of BPN was generated by the addition of amethyl group to the *N*-alicylic chain [5] (Tab. I).

The principal mechanism of BPN action *in vivo* is the interaction with the mineralized component of bone tissue, preventing bone reabsorption via inhibition of osteoclast precursors [2].

BPNs can be classified into 2 groups based on the structure of R2 side chains. Nitrogen containing BPNs (eg, alendronic acid, risedronic acid, zoledronic acid) are much more potent with regard to their bone antiresorptive activity than the non nitrogen-containing BPNs (eg, etidronic acid). Among the nitrogen containing BPNs, those with a tertiary nitrogen in a ring structure (heterocyclic N-BPs; eg, risedronic acid and zoledronic acid) have the highest potency, [6], inhibit the mevalonate pathway (i.e, the cholesterol synthesis pathway) and induce caspase activity [7] and are the strongest inhibitors of farnesyl pyrophosphate synthase, which is a key branch-point enzyme in the mevalonate pathway [8], partially explaining their anticancer effect. Zoledronic acid is the BP most extensively evaluated *in vitro* for its antitumor activity, including its effect on colon cancer cells. Osteonecrosis of the jaw has been reported among long term users of intravenous BPNs.

BPNs are hydrophilic molecules thereby not passing directly through biological membranes. Evidence suggests that BPNs are held in bone for several years even after the drug therapy is discontinued [9]. BPNs bind tightly to hydroxyapatite crystals situated in bone surfaces and there remain for long time, since they are not susceptible to enzymatic degradation by osseous pyrophosphatase. BPNs are constantly and gradually released from bone tissue into haematic circulation, entering in osteoclasts by endocytosis [10].

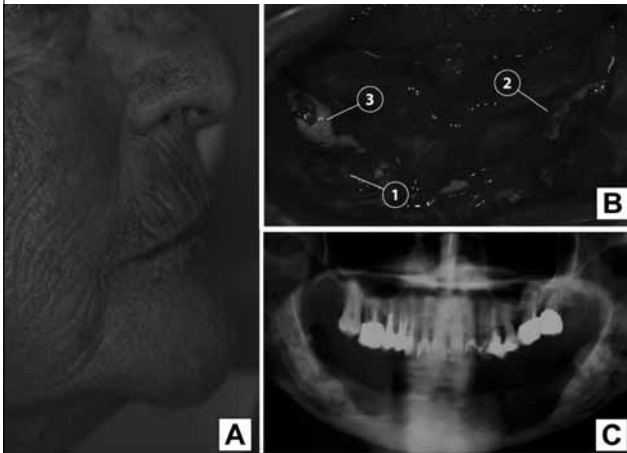
However, the etiopathogenic mechanisms of this pathological condition are poorly understood. Although, several pathways have been proposed for Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) occurrence, no single model can explain all morphological changes observed at the macro- and microscopic level. A recent research suggests that BPNs may promote an anti-angiogenic effect which contributes directly to the clinical features associated with BRONJ. Remarkably, the anti-angiogenic effect promoting BRONJ might be in keeping with the anti-neoplastic action of BPNs [11].

Recent studies revealed that BPNs induce osteoclast apoptosis by the farnesyl-diphosphate (FPP) synthase inhibition in the mevalonate pathway and subsequent accumulation of isopentenyl pyrophosphate [12]. BPNs inhibit osteoclast-mediated bone resorption and, consequently, the suppressive effect of BPNs on bone tissue renewal debilitate the bone by inhibiting the removal of damaged cells from normal bone and increasing bone mineralization [13]. This phenomenon, which recognizes the jawbone as target tissue, leads to ONJ with BPNs accumulation in skeletal sites for high bone turnover (Fig. 1). About 80% of ONJ cases reported heavy lesions, and 69% of cases occurred after alveolar surgery, such as tooth extraction. Painful symptoms are reduced during chronic phases of the pathology and granulation tissue appears to delimit inflammation areas. The possible formation of fistulous tissue allows spontaneous draining of the purulent exudate, reducing the edema by defining the osteonecrotic area (Fig. 1). ONJ is often asymptomatic for some time before clinical manifestation. As long as the overlying mucosa is intact and infection is not introduced into the bone, which has limited healing potential, there may be no clinical signs or symptoms of the underlying bone pathology [14].

#### THE EPIDEMIOLOGICAL RELEVANCE OF ONJ

Osteoporosis is an age-related disease that causes disability, deterioration in the quality of life, and high costs in terms of public health [15]. BPNs are used in the treatment of osteoporosis, and are taken by 73% of osteoporotic patients. Almost 190 million prescriptions of oral BPNs are dispensed worldwide each year [16]. The type of BPN used may play a role in the development of ONJ. This complication has been described after exposure to the nitrogen-containing BPNs pamidronate and zoledronic acid. Zoledronic acid presents a higher risk than pamidronate [17]. Probably because of the higher inhibitory effect of zoledronic acid on bone turnover compared with pamidronate. Furthermore, zoledronic acid causes greater reduction in collagen type-I degradation products (*N*-telopeptide) than pamidronate [18], confirming its greater antiresorptive activity. Wessel et al. indicate that zoledronate independently increases the risk of adverse effects; in fact, individuals undergoing zoledronate therapy exhibit a 30-fold increased risk of developing ONJ [19]. Despite, a recent study [20] shows that intravenous BPN therapy for osteoporosis

**Fig. 1.** Osteonecrosis of the jaw as induced by BPNs in an edentulous patient. Is reported an example of 80-year-old woman diagnosed with multiple myeloma was on long-term treatment with biphosphonates before developing ONJ in relation with dental extractions. (A) Sagittal view of the patient's profile. (B) Macroscopic appearance of oral osteonecrosis of the jaw. It can be seen that: 1) granulation tissue delimiting inflammation areas; 2) purulent exudate; 3) exposed osteonecrotic areas. (C) Bone loss in jaw is evident in particular in the lower right part of the Figure (panoramic x-Ray).



does not measurably increase the risk of ONJ among postmenopausal women. Among cancer patients receiving high-dose intravenous BPNs, it was estimated an ONJ incidence of 1-12% [21]. Carlson et al. found that patients with conditions requiring intravenous BPNs had a much higher risk of developing adverse conditions in the jaw compared with patients taking oral BPNs [22].

In fact at least 50% of intravenous BPNs is bio-available for incorporation into the bone matrix compared with an average of 1% of oral BPNs absorbed by the gastrointestinal tract [23]. Approximately 94% of all osteonecrosis cases are due to intravenous BPNs used and 6% are linked to oral BPNs [24, 25]. Among 368 cases of ONJ, 15 (4.1%) occurred in patients receiving BPNs to treat osteoporosis, considerably less than the 337 cases (91.6%) observed in patients receiving BPN to treat multiple myeloma, breast cancer, or prostate cancer. This difference is attributable to the different route of administration and dose used in these clinical situations, i.e., high dose parenteral administration in the context of cancer and low dose oral administration in the case of osteoporosis [25].

Lower ONJ incidence levels have been reported in those countries demonstrating a high level of health and oral hygiene (UK, Sweden) [26], suggesting an important role for bacterial infection as a contributing risk factor. Moreover, bacterial flora could produce septic conditions, involving bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It remains unclear whether infection plays a primary causative role or is secondary to the appearance of the lesion, and whether it initially arises in the bone or soft tissue [27].

Currently available published incidence data for BRONJ are based on retrospective studies and estimates of cumulative incidence range from 0.8 to 12% and 60-70% of cases are preceded by a dental surgical procedure [28]. A summary of ONJ risk factors related on BPNs is reported in Table II.

**Tab. II.** Risk factors identifying BPN-treated patients at high risk for developing ONJ following dental surgery.

Risk factor	Rank	Conferred risk	References
BPN administration route	intravenous > oral	High	[22, 25]
BPN type	Zoledronate > Pamidronate	High	[18, 19]
BPN dose	high > low	High	
BPN therapy duration	long > short	Medium	
Cause of BPN therapy	Cancer > osteoporosis	Medium	[20, 21]
BPN treatment cycles	18 cycles or more > 12 cycles or less	High	[62]
Oral hygiene	Poor > high	Medium	[26]
Cyclosporine therapy	Yes > no	Low	[41]
Antiangiogenic therapies (e.g. interferon, etc.)	Yes < no	Low	[45]
Smoking	Yes < no	Medium	[46]
Multiple myeloma	Yes < no	High	[27]
Systemic blood diseases and lymphomas	Yes < no	Medium	[27]
Autoimmune diseases	Yes > no	Low	[46]
Local radiotherapy	Yes > no	High	[3]
Local dental and periodontal diseases	Yes > no	Medium	[27, 49]
Obesity	Yes > no	Low	[19]
CYP2C8 gene polymorphism	TT homozygosity > heterozygosity and wild type	High	[51]
Prothrombin gene polymorphisms	G20210 > A	Low	[53]
Leiden V factor gene polymorphisms	Arg5406 > Gln	Low	[53]
Plasminogen-activating inhibitor-1 gene polymorphism	4G/4G homozygosity > heterozygosity and wild type	Low	[55]
Multidrug resistance gene 1 polymorphism	Exon 26: C3435 > T; Exon 21: G2677 > T/A	Low	[56]
TNF-alpha gene polymorphism	G307 > A	Low	[58]



### THE ROLE OF DENTAL PROCEDURES IN THE DEVELOPMENT OF ONJ

Dental trauma, such as dental extraction, is the most common risk factor for ONJ, although cases have occurred spontaneously [29]. In fact, while dental extraction greatly increases the need for repair of alveolar bone, the anti-resorptive function of BPNs may reduce the ability to perform this repair, thus causing ONJ. Disruption of blood flow could be another contributing factor [30]. Badros et al. [31] reported a significant association between the occurrence of ONJ in dental extraction ( $p = 0.009$ ) and age ( $OR = 1.09$ ;  $p = 0.003$ ) in patients with multiple myeloma receiving intravenous BPN treatment.

Implant therapy is not allowed, in patients who underwent intravenous BPNs. In contrast, surgery is usually not contraindicated with use of oral BPNs, but the patient should be informed of potential complication [32]. The jaw is highly susceptible to osteonecrosis because it is characterized by greater cellular turnover than the maxilla and other bones. Furthermore, the jaw has a terminal circulation, hampering the establishment of additional circulation during ischemic episodes. Ruggiero et al. highlighted ONJ prevalence in the jaw, its possible development from even simple surgical treatments, as well as it has a vascular nature and predisposing septic parameters. In parallel, chewing causes constant trauma to the jaw, and exacerbates the instability of localized microfractures, [33].

### OCCUPATIONAL RISK

In vivo studies show that BPNs have toxic and genotoxic power [34], and therefore should be considered as “dangerous drugs” during the preparation and handling. According to Polovich [35] “hazardous drugs” represents a potential health risk to health care workers who may be exposed during preparation or administration. These drugs require special handling because of their inherent toxicities. Drugs that meet one or more of the following criteria should be handled as hazardous [36].

- Carcinogenicity
- Teratogenicity or developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity

Structure or toxicity similar to drugs classified as hazardous using the above criteria.

Some of these features are typical of BPNs and therefore during the preparation and administration of these drugs should be taken preventive safety measures. Preventive measures such as: the use of disposable gowns, gloves, masks, shoe covers, and the use of vertical laminar flow hoods to maintain the sterility of the product and the protection of the work surface of the operator. The work surface must be free of materials, with the exception of BPN drugs and must be cleaned with 70% alcohol and moist paper (guidelines ASHP) [36]. Therefore, the workers handling the BPNs must undergo health surveillance pursuant to Legislative Decree 81/2008 on the

same basis in workers exposed to processing and handling of other dangerous drugs.

### Environmental mutagens and oral osteonecrosis

#### BIPHOSPHONATES AND DNA DAMAGE

BPNs realize their antiosteoclast effects through modification of the Rho family GTPases, which include Rac GTPases [37]. Deletion of *Rac1* gene results in a reduction of osteoclast formation because of its effects on pre-osteoclast chemotaxis, actin assembly, and RANKL-mediated reactive oxygen-species generation. *Rac1* deletion in knock-out mice increased trabecular-bone volume and trabecular number as compared with wild-type and *Rac2*-null mice [38].

Two aromatic bis-(2-chloroethyl) amino-bisphosphonic acids were investigated for their genotoxic potential as determined in *S. typhimurium* and mammalian cells *in vitro*. Both compounds induced a two-fold increase in *his+* revertants in *S. typhimurium* TA1535 following metabolic activation with subcellular liver fractions, thus demonstrating the mutagenic attitude of BPNs. *In vivo* toxicity and genotoxicity parameters were determined in liver and bone marrow cells after treatment. The genotoxicity of both compounds was exerted in several tissues but was lower in bone marrow cells than in liver cells [34].

BPNs induce apoptosis in osteoclasts but prevent apoptosis in osteoblasts. Both effects are related to BPNs binding to connexin 43. The prevention of osteoblastic apoptosis is mediated by Cx43 hemi channel opening and related activation of the extracellular signal-regulated kinases). However, Cx43, is also involved in BPNs pro-apoptotic effects in osteoclast [39].

#### EXOGENOUS RISK FACTORS FOR ORAL OSTEONECROSIS OTHER THAN BPNs: DRUGS, SMOKE, AND IONIZING RADIATION

Exogenous risk factors for ONJ include cigarette smoke, alcohol consumption, bacterial infections, and cyclosporine therapy. Endogenous risk factors include systemic diseases such as diabetes or hypertension and adverse polymorphisms of genes involved in metabolism such as CYPs, MTHFR.

Available molecular findings provide evidence that ONJ recognizes risk-factors associated with environmental mutagenesis and gene-environment interactions.

Glucocorticoid administration is a risk factor for osteonecrosis [40]. Calcineurin-inhibitors, particularly cyclosporine, may increase the risk of osteonecrosis because of vasoconstricting effects [41]. Cyclosporine is a cyclic hydrophobic endecapeptide derived from the metabolic products of two species of fungi, *Trichoderma polysporum* and *Cylindrocarpon lucidum*. The antimicrobial activity of cyclosporine is weak but this compound has a remarkable inhibitory effect on lymphocyte proliferation [42]. Cyclosporine inhibits many of the processes

involved in T-cell-mediated immune responses; in particular, a concentration of 10/20 ng/ml inhibits the synthesis of interleukin-2, limiting the amplification of cytotoxic T lymphocytes. Cyclosporine has a selective activity against T lymphocytes: T suppressor lymphocytes remain unaffected, while cytotoxic T lymphocytes and T helper cells are susceptible to drug. Cyclosporine is a widely used immunosuppressive agent, predominantly for transplant patients. It is well recognized that transplant patients are prone to developing squamous carcinoma of the skin and mucosa. Cyclosporine is a specific ligand for calcineurin, a ubiquitously expressed cellular serine/threonine phosphatase that plays important roles in the immune system and cardiac muscle. Many genes were identified to be responsive to cyclosporine treatment, including regulatory molecules involved in apoptosis, DNA damage repair, and cell-cycle regulation [43]. The mechanisms involved in the pathogenesis of cyclosporin A-induced gingival hyperplasia are not well understood. In mice treated intraperitoneally with increasing doses of cyclosporine A, oral mucosa has increased vascularity, thickening of the epithelial tissue and connective tissue, edema, mononuclear infiltrate and gingival hyperplasia [44]. Anti angiogenetic agents induce a risk of ONJ when administered concurrently with BPNs [45]. This situation frequently occurs in patient undergoing long-term treatment with interferon for chronic viral hepatitis or for anti-cancer therapies. Cigarette smoke is an extremely complex mixture of mutagens representing a risk factor for a variety of inflammatory, neoplastic, and vascular diseases. The direct effect of smoke on blood vessel significantly contribute to ONJ. In fact, smoke causes increased vasoconstriction and thrombosis in the bone, leading to ischemic states that may underlie the pathophysiology of osteonecrosis [46]. It has been demonstrated that smoke increase mtDNA deletion (common deletion 4977) in artery and inhibits the activator of plasminogen inhibitor 1 increasing the thrombosis risk [47].

In addition, ionizing radiation constitute a risk factor for ONJ [3]. In fact, 93% of patients with ONJ was previously treated with a radiotherapy regimen with doses of over 6,500 cGy. This leads to a adverse effects exerted by ionizing radiation towards bone tissue including clastogenic DNA damage, oxidative stress, stem cell depletion [3] (Tab. II).

### ONJ BIOMARKERS

The decreased serum levels of telopeptide type I collagen is a biological marker in ONJ. To validate this hypothesis, Bagan et al. compared 15 patients with bisphosphonate-induced ONJ to a control group of 10 healthy age- and gender-matched individuals [48]. Their preliminary results showed decreased telopeptide of type I collagen serum levels in patients with ONJ, but further studies containing a greater number of patients are needed to prove the utility of this finding as a biological and prognostic marker in ONJ [48].

## Endogenous risk factors and oral osteonecrosis

### SYSTEMIC AND LOCAL RISK FACTORS

ONJ may be associated with a number of different predisposing systemic conditions such as haemoglobinopathies, coagulopathies, lymphoproliferative disorders, Paget's disease, phosphorous exposure, and local conditions of sepsis (apical or periodontal), trauma (surgical or accidental) and radiotherapy. The exact role of these factors involved in the pathogenic process remains to be established [26]. Patients with multiple myeloma are at highest risk for ONJ, possibly due to inherent myeloma bone-metabolism abnormalities, such as increased activity of osteoclasts and inhibition of osteoblast function, leading to enhanced bone resorption.

Dental risk factors include periodontal disease, dental abscesses, surgical procedures involving the bone, and trauma from ill-fitting dentures, all of which may lead to mucosal lesions [26]. Oral conditions that predispose to tooth extraction, such as advanced caries, moderate to advanced periodontitis, and xerostomia, are indirect risk factors for ONJ [49]. The association of ONJ with poor dental health is established [50].

Obesity was also found to be associated with ONJ risk in cancer patients. Although it is currently unclear which pathway might cause an obese person to develop ONJ. In fact, obesity is potentially correlated with an increase in masticatory function that could lead to oral-bone microtraumas [19].

### GENE POLYMORPHISMS

Like other degenerative diseases, ONJ is caused by a combination of environmental and genetic risk factors. The potential role of genetics in the development of ONJ has been explored in multiple myeloma patients undergoing BPN therapy. Four single nucleotide polymorphisms (SNPs) were considered (*rs1934951*, *rs1934980*, *rs1341162*, and *rs17110453*) mapped within the cytochrome *P450-2C gene (CYP2C8)*. The analysis of SNP *rs1934951* and 3 additional SNPs allocated on the same gene (i.e. *rs1934980*, *rs1341162*, and *rs17110453*) highlights an over-representation of the homozygous TT genotype in cases as compared with controls. Thus, individuals homozygous for the TT genotype have an increased risk of developing ONJ (OR = 12.75) [51]. *CYP2C8* gene polymorphisms can affect several biologic pathways [52], which could be involved in the development of ONJ in patients treated with BPNs. Because ONJ is an avascular necrosis of the jawbone, the alteration of this pathway due to a variant of *CYP2C8* could make development of osteonecrosis. These results suggest that the *rs1934951* polymorphism on *CYP2C8* gene is a risk factor for ONJ. This information could help us to exclude patients at high risk from BPN therapy, and to take specific preventive measures.

Another study examined the association between osteonecrosis and thrombotic polymorphisms in genes encoding factor V Leiden and the prothrombin (*20210A*) gene

mutation. Factor V Leiden and the prothrombin *20210A* gene mutations occurred significantly ( $p = 0.006$ ) frequently in patients with osteonecrosis than in a population of 282 healthy volunteers ( $OR = 3.1$ ,  $95\% CI = 1.4-6.6$ ). This study suggests that coagulation abnormalities in the form of factor V Leiden and prothrombin *20210A* gene mutations might play a role in osteonecrosis [53]. Major thrombophilic mutations have been identified as risk factors for non-traumatic osteonecrosis in Caucasians. The factor V Leiden mutation was present in 18% of the patients compared with 4.6% of the control subjects, resulting in a statistically significant difference ( $OR = 4.5$ ). Factor V Leiden polymorphism is also associated with osteonecrosis of the femoral head [54]. Genetic studies in subgroups of patients with steroid-induced osteonecrosis focused on coagulation, fibrinolytic factors and homocysteine metabolism. A positive association of plasminogen-activating inhibitor-1 (PAI), MTHFR and factor V Leiden polymorphisms with steroid-induced ON was reported [55].

High plasma PAI-1 concentrations were associated with coronary artery disease and other thrombotic disorders. Regarding the effect of PAI-1 polymorphism on osteonecrosis, it has been reported that 4G/4G PAI-1 homozygosity is a risk factor for osteonecrosis [56]. It has been demonstrated that cigarette smoke is a potent inducer of PAI-1 gene expression [47] thus providing evidence for the interaction between smoking and an adverse genetic PAI-1 polymorphism as contributing to thrombosis and ONJ.

Polymorphisms in the multidrug resistance gene 1 (ABCB1), which encodes the drug-transport protein, P-glycoprotein leads to drug resistance to various agents, including steroids. It was found that the 3435TT exon 1 genotype had a protective effect against the development of ONJ. The same result was also observed with homozygosity in the mutant 2677T/A variants. As ONJ is a rare occurrence, systematic pharmacogenetic studies are needed to assess the possibility of genetic susceptibility [57]. The TNF cytokine is crucial to both immune and inflammatory responses. TNF up-regulates host defense mechanisms and also affects tissue physiology, including bone resorption, which is a crucial step in ONJ. Over-expression of TNF in the periodontium may be harmful to the host. Normally, TNF and other pro-inflammatory agents are regulated by IL-10, suggesting that some deficiency in this regulation mechanism may be linked to the disease. Although several polymorphisms have been reported in the *TNF-A* promoter, the majority of studies have been focused on the G/A polymorphism at position-307 because most of the other polymorphisms being functionally silent. TNF

adverse polymorphism increase the risk of periodontal bone loss [58] and periodontitis [59]. Main genetic polymorphisms representing risk factors for ONJ are listed in Table II.

## Conclusions

Risk factors of both exogenous and endogenous origin play an important pathogenic role in the development of ONJ. It is important to identify patients at high risk for developing ONJ after dental surgery. This approach should be useful to (a) identify those patients in which dental surgery could cause a risk rather than a benefit; (b) apply preventive intervention before dental surgery to decrease ONJ risk; (c) define time and type (less or more invasive) of surgical intervention. The American Dental Association has produced guidelines regarding the dental management of patients prescribed BPNs [60]. A recognized therapeutic protocol that allows for clear identification of BNP-related ONJ does not currently exist. Common guidelines present in the literature consist of a first approach to acute phases with broad antibiotic therapy and antimicrobial rinses such as 0.12% chlorhexidine, and, for second incidences, substitution with a specific therapy after the antibiogram.

Since the half-life of BPNs in human bone can reach more than 10 years [61] it has been generally questioned whether the interruption of BPNs will be of any benefit [62, 63]. Migliorati et al. suggest that, until prospective studies of BPN-related ONJ provide information about effective treatment protocols, the best approach is prevention, with the dental practitioner and the physician working collaboratively [64]. Translation of basic scientific findings into clinical practice is the essential premise for the development of future preventive strategies. Risk for ONJ appearance is greatly influenced by genotoxic factors related to oxidative damage such as those related to bacterial infections, inflammation, smoking, and ionizing radiation. Administration of chemopreventive drugs is a possible strategy to overcome this mechanisms in high risk patients, such an approach being usually referred as targeted chemoprevention [65, 66]. Furthermore BPN being mutagenic and genotoxic represent an occupational risk for workers involved in their production and administration thus have to be considered "hazardous drugs".

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# Health workers sensitization: effects on perceived quality of immunization services among mothers of under five children in Ilorin, North Central Nigeria

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## Key words

Perceived quality • Immunization services • Health Workers Sensitization • Nigeria

## summary

*Clients' satisfaction with services received is an important dimension of evaluation that is examined only rarely in developing countries. Health care professionals have always acknowledged that satisfying the consumers at some level is essential to providing services of high quality. This is a quasi-experimental study. The study group included 150 mothers bringing their children for immunization at Alanamu Health Centre, Ilorin. The control group included 150 mothers bringing their children for immunization at Okelele Health Centre. Total population of mothers bringing their children for vaccines against tuberculosis/poliomyelitis/hepatitis B (BCG/OPV/HBV) and against diphtherite-pertussis-tetanus (DPT)/OPV/HBV were recruited sequentially until sample size was attained. Mean waiting time at pre-intervention was  $82.7 \pm 32.5$  and  $90.4 \pm 41.7$  minutes for the study and control groups respectively.*

*Post intervention, there was a significant decrease ( $p < 0.05$ ) in the estimated waiting time in the study group (mean =  $48.0 \pm 24.4$  minutes) while there was no observed difference in the control  $p > 0.05$  (mean =  $88.4 \pm 40.6$  minutes). Perceived adequacy of information on services being provided by the health facility was low (58%) in the study group while it was relatively higher in the control group (80%), but there was a significant increase in proportion of those that felt information was adequate only in the study group ( $p < 0.05$ ) at post intervention. Waiting time in health facilities by clients should be reduced as this may give clients a positive perception of the service they have come to access. Information dissemination to clients should be encouraged among health workers as this would affect clients' knowledge and also quality of health care delivery.*

## Introduction

The view that consumers should have information and other resources necessary to make judgment about the value of goods and services pervades all other sectors of our society and is bound to influence health care eventually. One manifestation of this view is the concept of "consumer – centered care" [1]. Scientific development has fostered the growing emphasis on the importance and legitimacy of clients' perspective on the quality of service [2].

Clients' satisfaction with services received is an important dimension of evaluation that is examined only rarely in developing countries [3]. Health care professionals have always acknowledged that satisfying the consumers at some level is essential to providing services of high quality. At the same time however, health care professionals have often discounted the importance of clients' perspectives in the belief that clients' have very limited knowledge of what constitutes technical quality [3]. Although the perspective of the health care professionals is widely acknowledged to be important, other perspectives on quality have been emphasized in recent years. The most important change has been a growing recognition and insistence that services must be tailored towards the preferences and values of the con-

sumers especially individual opinion about services as this is an important indicator of its quality [4].

Clients' tend to be critical of poor communication and provision of information from health professionals [5]. Dissatisfaction with primary care services lead many people to turn to higher level hospitals for primary care [6]. Service marketing researchers suggest that the physical environment, the people and processes strongly affect consumers' judgment when they evaluate services. Consumers make judgment about quality of services by assessing factors they can appraise such as courtesy, responsiveness, attentiveness and perceived competence; waiting time after arrival at the health centre and duration of examination [7-9]. The information from which inferences can be drawn about quality of services can be classified under three categories: Structure, process and outcome [10, 11]. Structure denotes the attributes of the settings in which care occurs. This includes the attributes of material resources (such as facilities, equipment and money), of human resources (such as number and qualifications of personnel), and of organizational structure (such as medical staff organization, methods of peer review, and methods of reimbursement) [12, 13].

Process denotes what is actually done in giving and receiving care i.e. the technical competence and the interpersonal process/relationship [12, 13]. Outcome refers

to the effects of care in the health status of patients and populations. Improvement in the clients' knowledge and salutary changes in their behaviour are included under the broad definition of health status; it also includes clients' satisfaction with services [12, 13].

This study was carried out to determine the effects of health workers sensitization on the perceived quality of immunization services among mothers of under children in Ilorin North Central Nigeria.

## Materials and methods

Ilorin can be described as an emerging city with a projected population of 805, 396 [14]. Children under five years of age constitute about 13.12% of the population [15]. Alanamu Health Centre, where the study was conducted, is a primary health facility located in Ilorin West LGA. It serves as a fixed site for immunization and it provides other services such as maternal services, family planning, growth monitoring, food demonstration and general outpatient consultations. The control site is at the Okelele Health Center located in Ilorin East LGA. It is also a fixed site for immunization and provides similar services to the study site.

This is a quasi-experimental study that was carried out in three stages: Pre-intervention, intervention and post-intervention stages. At Pre-Intervention, exit interview with mothers of children was conducted using a pre-tested structured questionnaire that was administered to both the study and control groups to generate quantitative data.

At Intervention, there was sensitization of health workers at Alanamu Health Centre where the study group was. The health workers sensitized were nurses, Community Health Officer (CHO) and Community Health Extension Workers (CHEWs) because they were the ones involved in immunization. The sensitization involved all 18 health workers in the facility over the span of two days. The sensitization focused on improving quality of immunization services at the health center based on findings from the perspectives of mothers of children attending the immunization clinic (findings were from the data collected at the pre-intervention).

The post intervention was carried out three months after the intervention to allow possible changes to occur in quality of service delivery. The same questionnaire used in the pre-intervention stage was administered again as exit interviews to both study and control groups to evaluate the effects of sensitization of health workers on the quality of service provided at the immunization clinic of the health facilities as perceived by mothers. The same mothers interviewed at the pre intervention were interviewed at post intervention in both the study and the control groups.

The study and control groups each included 150 mothers bringing their children for immunization at the health centres. Total population of mothers bringing their children for vaccines against tuberculosis/poliomyelitis/hepatitis B (BCG/OPV/HBV) and against diphtherite-pertussis-tetanus (DPT)/OPV/HBV were recruited sequentially until sample sizes were attained. This made

it easier to get a cohort of mothers attending the clinic at the same time and who will be due for revisit at the same time.

The analysis was done using SPSS version 16. Two-staged analysis was done; analysis of the pre-intervention questionnaires and the post-intervention questionnaires. McNemar's Chi-square test was used to compare proportions. Mann Whitney U test was used to test whether the two groups are significantly different from each other with regards to waiting time at the clinics. A p-value of less than 0.05 was considered as statistically significant.

Ethical approval for the study was obtained from the ethical committee of the University of Ilorin Teaching Hospital. Mothers' consent was obtained before interview and nature of study was made clear. For ethical reasons, sensitization was carried out at Okelele health centre after the post intervention data had been collected

## Results

The socio-demographic characteristics (Tab. I) of both the study and control groups were similar as there were no significant differences in their socio-demographic characteristic ( $p > 0.05$ ). Many of the respondents (54.0% of the study group and 53.3% of the control group) estimated that they waited  $> 60$  minutes before they were attended to by health workers at pre-intervention (Tab. II). Mean waiting time at pre-intervention was  $82.7 \pm 32.5$  and  $90.4 \pm 41.7$  minutes for the study and control groups respectively. Post intervention, there was a significant decrease ( $p < 0.05$ ) in the estimated waiting time in the study group (mean =  $48.0 \pm 24.4$  minutes) while there was no observed difference in the control (mean =  $88.4 \pm 40.6$  minutes). At pre-intervention, 60 (40%) of the respondents in the study group felt the waiting time was too long, while 49 (32.7%) of control felt same but there was a significant decrease ( $p < 0.05$ ) in the number of the study group respondents that felt the waiting time was too long at post intervention (Tab. II). There was no observed difference among the control group at post-intervention.

About 43.3% and 36.7% of respondents in the study and control groups respectively were not told the number of immunizations they were to take to complete the schedule at pre-intervention but at post intervention there was a significant decrease in those that were not told the number of visits left to complete the schedule ( $p < 0.05$ ) in the study group. This difference was not observed in the control group (Tab. III).

Generally, greater than 70% of respondents in both study and control groups felt the information they had received on immunization was adequate though there was a significant increase ( $p < 0.05$ ) in the proportion that felt information was adequate in the study group only at post intervention (Tab. III).

Perceived adequacy of information on other services being provided by the health facility was low (58%) in the study group while it was relatively higher in the

Tab. I. Sociodemographic characteristics of respondents.

Variables	Study group (%) (N = 150)	Control group (%) (N = 150)	$\chi^2$ p-value df
<b>Age group</b>			
16-20	4 (2.7)	6 (4.0)	$\chi^2 = 1.48$ $p = 0.9157$ df = 5
21-25	41 (27.3)	40 (26.7)	
26-30	63 (42.0)	58 (38.7)	
31-35	26 (17.3)	26 (17.3)	
36-40	12 (8.0)	13 (8.7)	
> 40	4 (2.7)	7 (4.6)	
<b>No of children</b>			
1	33 (22.0)	36 (24.0)	$\chi^2 = 0.28$ $p = 0.9633$ df = 3
2	39 (26.0)	40 (26.7)	
3	37 (24.7)	34 (22.7)	
> 3	41 (27.3)	40 (26.6)	
<b>Occupation</b>			
Trader	64 (42.7)	80 (53.3)	$\chi^2 = 10.42$ df = 6 $p = 0.1081$
Tailor	34 (22.7)	26 (17.3)	
Housewife	11 (7.3)	7 (4.7)	
Civil servants	8 (5.3)	1 (0.7)	
Teaching	6 (4.0)	5 (3.3)	
Student	6 (4.0)	4 (2.7)	
Others	21 (14)	27 (18.0)	
<b>Level of education</b>			
None	55 (36.7)	56 (37.3)	$\chi^2 = 0.43$ df = 3 $p = 0.9334$
Primary	59 (39.3)	62 (41.4)	
Secondary	25 (16.7)	21 (14.0)	
Post secondary	11 (7.3)	11 (7.3)	
<b>Ethnicity</b>			
Yoruba	124 (82.7)	135 (90.0)	$\chi^2 = 3.42$ df = 2 $p = 0.1804$
Fulani	17 (11.3)	10 (6.7)	
Others	9 (6.0)	5 (3.3)	
<b>Religion</b>			
Christianity	24 (16.0)	12 (8.0)	$\chi^2 = 3.82$ $p = 0.0507$
Islam	126 (84.0)	138 (92.0)	
<b>Marital status</b>			
Single	5 (3.3)	9 (6.0)	$\chi^2 = 0.67$ $p = 0.4115$
Married	145 (96.7)	141 (94.0)	

control group (80%), but there was a significant increase in proportion of those that felt information was adequate only in the study group ( $p < 0.05$ ) at post intervention (Tab. III).

In the study group, less than 50% of respondents received all immunization due for that visit while more than 80% received all vaccines due for visit in the control group. There was no significant increase in both study and control groups at post intervention. About 62.7% and 60.8% of respondents in the study and control groups had correct knowledge of number of visits left to complete the immunization schedule at pre intervention but there was a significant increase in those that had correct knowledge of number of visits left to complete the schedule in the study group ( $p < 0.05$ ) at post-intervention. There was no significant increase in those that had correct knowledge of immunization visits left to complete the schedule in the control group at post-intervention (Tab. IV).

Also, all respondents 150 (100%) in the study and control groups had injection site cleaned before injection was administered at pre intervention and post intervention. About 90% of respondents in the study group and 85% of the control group had paid for the service at pre intervention and the proportion did not increase significantly at post intervention in both study and control groups ( $p > 0.05$ ). More than 80% of respondents in both study and control groups felt the amount paid was not too much and there was no significant difference in their perception at post intervention in both study and control groups ( $p > 0.05$ ) (Tab. V).

At pre-intervention more than 80% of respondents (in both study and control groups) had rated the health workers as treating them with respect, polite and approachable. Only 0.7% of respondents in both groups had rated the health workers as rude. There was however a significant increase in the proportion of respondents that rated health workers as approachable in the study group only



**Tab. II.** Distribution of respondents by their estimated waiting time and perception of waiting time.

	STUDY GROUP		CONTROL GROUP	
	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)	Pre-intervention N = 150 (%)	Post -intervention N = 150 (%)
<b>Waiting time (minutes)</b>				
< 31	15 (10.0)	21 (14.0)	22 (14.7)	20 (13.4)
31-60	54 (36.0)	74 (49.3)	48 (32.0)	54 (36.0)
61-90	38 (25.4)	49 (32.7)	38 (25.3)	32 (21.3)
> 90	43 (28.6)	6 (4.0)	42 (28.0)	44 (29.3)
	P = 0.0000, $\chi^2 = 33.45$ , df = 3		P = 0.7991, $\chi^2 = 1.01$ , df = 3	
<b>Time too Long</b>				
Yes	60 (40.0)	12 (8.0)	49 (32.7)	46 (30.7)
No	90 (60.0)	138 (92.0)	101 (67.3)	104 (69.3)
	$\chi^2 = 40.37$ , df = 1, p = 0.0000		$\chi^2 = 0.06$ , df = 1, p = 0.8040	

**Tab. III.** Distribution of respondents' by those that received information on immunization.

Variable	STUDY GROUP		CONTROL GROUP	
	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)
<b>Told immunization due for today</b>				
Yes	85 (56.7)	143 (95.3)	95 (61.3)	109 (72.7)
No	65 (43.3)	7 (4.7)	55 (36.7)	41 (27.3)
	$\chi^2 = 59.38$ , df = 1, p = 0.0000		$\chi^2 = 2.59$ , df = 1, p = 0.1076	
<b>Told when to return for next immunization</b>				
Yes	125 (83.3)	145 (96.7)	110 (73.3)	109 (72.7)
No	25 (16.7)	5 (3.3)	40 (26.7)	41 (27.3)
	$\chi^2 = 13.37$ , df = 1, p = 0.0002		$\chi^2 = 0.00$ , df = 1, p = 1.0000	
<b>Need more information on immunization</b>				
Yes	39 (26.0)	17 (11.3)	45 (30.0)	41 (27.3)
No	111 (74.0)	133 (88.7)	105 (70.0)	109 (72.7)
	$\chi^2 = 9.68$ , df = 1, p = 0.0019		$\chi^2 = 0.15$ , df = 1, p = 0.7017	
<b>Received enough information on other services</b>				
Yes	87 (58.0)	116 (77.3)	120 (80.0)	133 (88.7)
No	63 (42.0)	34 (22.7)	30 (20.0)	17 (11.3)
	$\chi^2 = 11.94$ , df = 1, p = 0.0005		$\chi^2 = 3.63$ , df = 1, p = 0.0566	

at post intervention ( $p < 0.05$ ). Seats were available for majority of the respondents in the study group (97.3%) and all respondents in the control group (100%) had seats available to them at the pre-intervention stage. At the post intervention stage all respondents in both study and control groups were offered seats (Tab. VI).

## Discussion

Previous studies assessing patients' perception of quality of health care have reported long waiting time (occasionally some researchers described the long waiting time as unacceptable) and this study is in agreement with such studies [8, 16-18]. The waiting time ranged between 20mins – 3hrs for the study group (mean =  $82.7 \pm 32.5$ mins) and 20 mins – 3½ hrs for the control group (mean =  $90.4 \pm 41.7$  mins) at the pre-in-

tervention stage. At post intervention, there was a significant reduction in waiting time for the study group ( $p < 0.05$ ) while there was no significant difference in waiting time of the control group ( $p < 0.05$ ). Akande et al in a study in Ilorin, Nigeria, documented estimated mean waiting time by patients to be 49.1 mins [17]. In other developing countries as Trinidad and Tobago, estimated waiting time to see doctors by patients ranged from 1-6 hours with a mean of 2 hours 40 minutes [8]. Studies carried out in rural Bangladesh indicated an estimated waiting time of  $30 \pm 2.5$  mins [16]. The waiting time would be different in various situations since the patients have come to access different services. At the pre-intervention stage, only 40% and 32.7% of the study and control group respectively felt the waiting time was too long. Ademola-Popoola et al reported a higher figure, stating 89.4% of respondents at the eye clinic perceiving the waiting time to be too long [18].

**Tab. IV.** Distribution of respondents by those that received all immunization due for that visit.

Child received all immunization due	STUDY GROUP		CONTROL GROUP	
	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)
Yes	73 (48.7)	90 (60.0)	121 (80.7)	128 (85.3)
No	77 (51.3)	60 (40.0)	29 (19.3)	22 (14.7)
	$\chi^2 = 3.44, df = 1, p = 0.0637$		$\chi^2 = 0.85, df = 1, p = 0.3564$	
Knowledge of visits left to complete the schedule	94 (62.7)	130 (86.7)	91 (60.6)	102 (68.0)
Correct	35 (23.3)	11 (7.3)	22 (14.7)	18 (12.0)
Incorrect	21 (14.0)	9 (6.0)	37 (24.7)	30 (20.0)
I don't know	$\chi^2 = 23.11, df = 2, p = 0.0000$		$\chi^2 = 1.76, df = 2, p = 0.4151$	

**Tab. V.** Distribution of respondents' by those that paid for the service and perception of amount paid.

	STUDY GROUP		CONTROL GROUP	
	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)	Pre -intervention N = 150 (%)	Post-intervention N = 150 (%)
Paid for the service received	136 (90.7)	137 (91.3)	128 (85.3)	131 (87.3)
Yes	14 (9.3)	13 (8.7)	22 (14.7)	19 (12.7)
No	$\chi^2 = 0.0, df = 1, p = 1.0$		$\chi^2 = 0.11, df = 1, p = 0.7367$	
Amount Too Much	23 (16.4)	21 (14.0)	20 (15.2)	21 (14.0)
Yes	117 (83.6)	129 (86.0)	112 (84.8)	129 (86.0)
No	$\chi^2 = 0.17, df = 1, p = 0.6801$		$\chi^2 = 0.01, df = 1, p = 0.9163$	

Report from Trinidad and Tobago states 48% of patients perceived the waiting time to be too long [8]. In Bangladesh, the patients reported that they would be satisfied with the waiting time if it is between 10-11 minutes.

At post intervention stage, there was a significant difference in their perception of the waiting time ( $p < 0.05$ ) as majority of them felt the waiting time was not too long. There was no significant difference observed in the control group. Patient wait times are inevitable but their reduction or elimination is an important marketing tool. Patients feel increased time demands and if waiting is too long, they may not come back. However if waiting times are reasonable and handled well, patients are more likely to have a positive perception of services and return to the practice. Timely health care service is very important in the provision of quality care which in turn will most likely improve the utilization of health services [19, 20].

Scientists especially in the field of medicine have been described as being deficient in communication and effective dissemination of information [5, 21]. In this study, less than 85% of mothers in both study and control groups received information on immunization at the pre-intervention stage. This also reflected in those that knew the number of visits left to complete their immunization schedule (pre-intervention). As less than 65% of both study and control groups knew exactly how many visits were left to complete the immunization schedule. This is similar to previous finding in Ilorin where 62.9% of mothers knew they were required to attend five times to get their children fully immunized but knowledge on when to return was low [22].

Despite the fact that less than 65% of respondents (both study and control at pre-intervention) knew exactly the number of visits left to complete schedule, majority of them (at least 70% in both study and control groups) felt the information they received on immunization was adequate. This may suggest that they are not likely to complete the immunization schedule, thereby increasing drop-out rates.

Ademola-Popoola et al reported that 83.6% of patients reported information on their ailment to be adequate [18]. An Istanbul study on antenatal care reported greater than 70% of respondents indicating they had received information on pregnancy [23]. Akande reported contrary findings in a study where 42.2% of respondents felt they received adequate information on the nature of their ailment from the health workers [24]. The nature of services a client demands to an extent may seem to affect this since those coming for immunization and antenatal are not primarily ill.

At post intervention stage, 88.7% and 72.7% of study and control groups respectively felt the information they received on that visit was adequate. This increase in the study group was statistically significant  $p < 0.05$  but the increase was not significant in the control group. This may suggest that patients may at times conclude that whatever care they receive is adequate when it is the norm but that an improvement on the care can also be perceived by patients.

If clients attending a particular facility do not know the services available, they are not likely to access all the services being rendered. In this study, only 58.0% of the study group (at pre-intervention) felt they received ad-

Tab. VI. Distribution of respondents by the perceived way they were treated by the health workers.

Assessment of treatment by health worker	STUDY GROUP		CONTROL GROUP	
	Pre-intervention N = 150 (%)	Post-intervention N = 150 (%)	Pre-intervention N = 150 (%)	Post-intervention N = 150 (%)
<b>Treated with respect</b>				
Yes	131(87.3)	141(94.0)	127(84.7)	131(87.3)
No	19(12.7)	9(6.0)	23(15.3)	19(12.7)
	$\chi^2 = 3.19$ df = 1 $p = 0.0741$		$\chi^2 = 0.25$ df = 1 $p = 0.6177$	
<b>Staff polite</b>				
Yes	143(95.3)	149(99.3)	148(98.7)	148(98.7)
No	7(4.7)	*1(0.7)	*2(1.3)	*2(1.3)
	$\chi^2 = 3.21$ df = 1 $p = 0.0732$		$\chi^2 = 0.25$ df = 1 $p = 1.0000$	
<b>Staff approachable</b>				
Yes	135(90.0)	146(97.3)	141(94.0)	147(98.0)
No	15(10.0)	*4(2.3)	9(6.0)	*3(2.0)
	$\chi^2 = 5.62$ df = 1 $p = 0.0178$		$\chi^2 = 2.17$ df = 1 $p = 0.1407$	
<b>Staff rude</b>				
Yes	*1(0.7)	*0	*1(0.7)	*0
No	149(99.3)	150(100)	149(99.3)	150(100)
	$\chi^2 = 0.0000$ df = 1 $p = 1.0000$		$\chi^2 = 0.0000$ df = 1 $p = 1.0000$	
<b>Staff indifferent</b>				
Yes	13(8.7)	15(10.0)	7(4.7)	*3(2.0)
No	137(91.3)	135(90.0)	143(95.3)	147(98.0)
	$\chi^2 = 0.04$ df = 1 $p = 0.8427$		$\chi^2 = 0.93$ df = 1 $p = 0.3346$	
<b>Seats Available</b>				
Yes	146(97.3)	150(100)	150(100)	150(100)
No	4(2.7)	0(0)	0(0)	0(0)

\* Represents where values were less than 5 and Yates correction was used.

equate information on other services while 80% of the control group (at pre-intervention) felt they received adequate information on other services that are provided in the facility. However, at post-intervention, there was a significant increase in proportion of mothers who felt information on other services was adequate ( $p < 0.05$ ) in the study group compared to the control group where there was no statistically significant increase  $p > 0.05$ . Generally, a high number of patients (51.3 and 40%) in the study group did not receive all vaccines due for the visit at the pre and post intervention respectively. Greater proportion (80.7 and 85.3%) of children received all vaccines due for the visit in the control group at pre and post intervention respectively. The reason may not be far fetched as health workers in the study group had reported shortages in supply of some vaccines and the two health facilities got their supply of vaccines from different cold store since they were situated in different LGAs. There was however no significant increase in the proportion of those that received all vaccines at post intervention. Unavailability of vaccines will in no doubt increase missed opportunities. The sensitization did not have remarkable change in the availability of vaccines because the supply of vaccines as a factor in quality

of care is beyond what the health workers in the study group facility could achieve on their own. Distribution of vaccine is through the Federal /state / Local Government cold stores to public and private health facilities and provision is through partnerships with international community and voluntary organizations [25]. In this study, 97.3% of mothers had seats available for them at the pre-intervention stage while 100% of those in control group had seats available to them. At post intervention, 100% of the mothers in study group had seats. This confirms reports from the health workers in Alanamu health centre that seats were inadequate. Mothers were also of the opinion that sitting was inconvenient as there were insufficient seats. This finding is higher than findings in Tanzania where only 89% of patients attending Antenatal care in public health facilities had seats available to them while 93% of those attending private hospitals had seats available for them [26]. This may suggest that facilities available at health facilities are inadequate for clients that patronize the services or that there are deficiencies in organization of such services. In this study, greater than 80% of both the study and control groups felt the health workers treated them with respect, were polite and approachable at both the pre-intervention

and post intervention stage. At post intervention however, there was a significant increase ( $p < 0.05$ ) in the study group of mothers who felt the health workers were approachable. There was no significant increase in the control group. This finding is not in agreement with an earlier finding where health workers confirmed that patients perceived the service they received as uncaring and sometimes punitive [27].

About 85% of respondents (in both study and control groups) had paid for the service they had received at pre and post intervention with no significant difference in proportion of those that paid. Immunization services according to the National Programme for Immunization is free in public health facilities but health workers have reported shortages in supply of some of the consumables for which they have to take a token amount from the mothers in order for the children to have their immunization up to date [25].

Majority of the mothers (80%) felt the amount paid was affordable. Affordability is relatively high for this service because it is a preventive service for which a lot of input into the service is provided by government and donor agencies. A recent study in an eye clinic also indi-

cated that 77.2% of patients felt the cost of eye treatment was affordable [18]. Affordability of cost of service will therefore depend on the kind of service that is sought by the patient. The eye clinic study may also share the same opinion, as 48% of those who considered the service unaffordable felt the surgical operations were unaffordable [18].

There was a significant increase in the proportion of mothers that perceived the information they have received both on immunization and other services to be adequate ( $p < 0.05$ ). A significant proportion of the mothers perceived the health workers to be approachable ( $p < 0.05$ ) at post-intervention.

Based on these findings, it can be concluded that sensitization of health workers affected mothers' perception of waiting time and adequacy of information received. Waiting time in health facilities by clients should be reduced as this may give clients a positive perception of the service they have come to access. Information dissemination to clients should be encouraged among health workers as this would affect clients' knowledge and also quality of health care delivery.

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# Personal hygiene among primary school children living in a slum of Kolkata, India

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## Key words

Primary school children • Personal hygiene • Maternal literacy • Slum • India

## Summary

**Introduction and objectives.** For children, maintenance of personal hygiene helps to improve the quality of life and longevity. This is of particular importance in a slum community with compromised living situation. This study was undertaken to find out the knowledge and practice of personal hygiene among the primary school children living in a slum area, to identify any misconception among them regarding the maintenance of personal hygiene, to find out their morbidity pattern, and also to elicit the relationship between practice of personal hygiene among the children and the literacy status of their mother.

**Methods.** A cross-sectional observational study was conducted among 104 primary school children of a primary school situated in the slum area of Chetla, Kolkata, India with the help of a pre-designed, pre-tested and structured questionnaire. Data were analyzed statistically by simple proportions and tests of significance.

**Results.** It was found that the female students were more knowledgeable than the male students regarding the maintenance of personal hygiene. There was a wide gap between practice and knowledge of personal hygiene among the primary school children living in the slum area. Even, misconceptions do exist on certain indicators of personal hygiene among the students. Statistically significant association was observed between practices of personal hygiene among the primary school children and the literacy status of their mother.

**Discussion and conclusions.** Future of a society depends considerably on the health of its children. The parents and the school teachers, as constructive shapers of children's health behaviors, should play a responsible role in early education of children on personal hygiene.

## Introduction

The foundations of lifelong responsibility for the maintenance of personal hygiene are laid down in childhood, which is important for a healthy childhood, for a healthy adulthood and for the development of positive values about health and the use of health services.

Poor health among school children is resulted from the lack of awareness of the health benefits of personal hygiene. Diarrhoeal diseases, skin diseases, worm infestations and dental diseases are most commonly associated with poor personal hygiene. One of the major problems faced by school children are infections. The primary causes of infections are contaminated water and poor sanitation, as well as poor hygienic practices. Lack of personal hygiene coupled with poor sanitation favor person-to-person transmission of infection. Infection and malnutrition form a vicious circle and retard children's physical development. Repeated attacks of infections often compound the existing poor health of children, compromising children's attendance and performance at school and not uncommonly, can result in death [1]. The condition may even be worse in a slum community with poor socio-economic condition and compromised living situation. The origins of many of the illnesses of adulthood also have their roots in the health behaviors of childhood and adolescence. How-

ever, majority of the childhood illnesses are preventable by promotion of hygienic practices among school children through proper health education by their parents and teachers.

Children in their primary schooling age can learn specific health-promoting behaviors, even if they do not fully understand the connections between illness and behavior [2]. Health habits can be developed in this period. More research on this ground is needed. The present inadequate knowledge base hinders the development of improved strategies for enhancing the maintenance of personal hygiene, which is of great importance to decrease the burden of communicable diseases in the developing countries.

With the above background, this study was undertaken with the following objectives:

- 1) to find out the knowledge and practice of personal hygiene among the primary school children living in a slum area;
- 2) to identify misconceptions among the study population regarding the maintenance of personal hygiene, if any;
- 3) to find out the morbidity pattern of the study population;
- 4) to elicit the relationship between practice of personal hygiene among the primary school children and the literacy status of their mother.

## Materials and methods

*Type of study.* Community based cross-sectional observational study.

*Place of study.* One purposively selected primary school situated in a slum under the service area of Urban Health Center, Chetla, Kolkata, India.

*Duration of study.* Two months.

*Study population.* All primary school children in grades I to V from the selected school, where the students come mainly from the neighboring slum locality.

*Study tool.* A pre-designed, pre-tested and structured questionnaire.

*Methodology.* Permission was obtained from the school authority. The questionnaire was drawn up in English, translated in Bengali (local language) and back translated in English to check the translation. Before starting of the study, pre-testing of the questionnaire was done in a different school situated in the same slum locality and accordingly necessary modifications were made and this was finalized. The selected school was visited on a pre-assigned day of each week and one grade was covered every week. There were average of 24-26 students enrolled per grade. The students from each grade who were absent on the specific day of the study were excluded. Thus, after excluding 21 absentees, a total of 104 students were finally included in the study. The response rate was 83.2%. The parents were invited on the specific days of the study. The class teacher of each grade was explained the purpose of the study. Good rapport was built up with the students and informed verbal consent was obtained from them and one of their parents. Briefing was done regarding the questionnaire provided to the students and they were asked to mark the responses. The questionnaire consisted of socio-demographic information, e.g. age, grade, sex, religion, literacy status of both mother and father, questions regarding knowledge and practice of personal hygiene, any misconception regarding personal hygiene, and lastly any illness over last 15 days among the primary school children. The questionnaire covered the following indicators of personal hygiene, i.e. combing hair, studying under adequate light, brushing teeth, washing mouth after eating, washing hands before eating, washing hands after visiting toilet, trimming nails, taking bath daily, wearing shoes and wearing clean clothes. Each student was also observed thoroughly to assess their status of personal hygiene, i.e. cleanliness of clothes, condition (clean and trimmed) of fingernails and toenails, cleanliness of teeth, condition (clean and combed) of hair, presence of shoes, etc. It was found that the observations were consistent with the responses of the students regarding personal hygiene practices. The morbidities listed in the questionnaire were fever with or without cough / cold, diarrhoea, passage of worms in stool, head lice, dental caries, scabies and multiple boils. The students were also examined clinically (general and systemic examinations) for the presence of signs of any illness, mainly to correlate with their reported illnesses. At the end of the study, the parents were given information about their children's status of personal hygiene and related health condition and suggested to contact the urban health center if needed. A brief health education session was also conducted for the class teachers, students and their parents after completion of the study.

*Analysis of data.* Data obtained were collated and analyzed statistically by simple proportions and tests of significance (Z-test and chi-square test), as and when necessary.

## Results

This study shows that the age of primary school children ranged from 5 to 14 years, maximum number (84) of students (80.77%) being between 7 to 12 years. Among 104 students, male and female students were 43 (41.35%) and 61 (58.65%), respectively. Maximum students (76) were Hindus (73.08%) and rests (28) were Muslims (26.92%). Estimates of maternal and paternal literacy were 31.73% (33 out of 104 mothers) and 69.23% (72 out of 104 fathers), respectively.

**Tab. I.** Distribution of students according to practice and knowledge of personal hygiene (n = 104).

Personal hygiene	Male (n <sub>1</sub> = 43)	Female (n <sub>2</sub> = 61)	Hindu (n <sub>c1</sub> = 76)	Muslim (n <sub>c2</sub> = 28)	Total (104)
Practice (score)					
Poor (< 8)	7 (16.28)	12 (19.67)	11 (14.47)	8 (28.57)	19 (18.27)
Good (8-12)	21 (48.84)	28 (45.90)	39 (51.32)	10 (35.71)	49 (47.12)
Very good (13-15)	12 (27.90)	15 (24.59)	19 (25.00)	8 (28.57)	27 (25.96)
Excellent (16-20)	3 (6.98)	6 (9.84)	7 (9.21)	2 (7.14)	9 (8.65)
Z <sup>*</sup> (Significance, p-value)	0.06 (Not significant, p > 0.05)		0.81 (Not significant, p > 0.05)		-
Knowledge (score)					
Poor (< 4)	14 (32.56)	9 (14.75)	17 (22.37)	6 (21.43)	23 (22.12)
Good (4-6)	28 (65.12)	50 (81.97)	57 (75.00)	21 (75.00)	78 (75.00)
Very good / Excellent (7-10)	1 (2.32)	2 (3.28)	2 (2.63)	1 (3.57)	3 (2.88)
Z <sup>*</sup> (Significance, p-value)	-2.11 (Significant, p < 0.05)		-0.19 (Not significant, p > 0.05)		-

Figures in the parentheses indicate percentages; \* Z-tests were done between the respective average scores.

Regarding practices of personal hygiene among primary school children, a score = 0 corresponded to “never practicing / incorrect practice”; a score = 1, to “sometimes practicing”; and a score = 2, to “practicing most of the times / regularly”. Therefore, overall, the maximum and minimum possible scores, based on 10 indicators of personal hygiene as considered in this study, were 20 and 0, respectively. Poor score was considered to be a score < 8 (i.e. < 40%), and other scores categorized were good score 8-12 (i.e. 40-60%), very good score 13-15 (i.e. 65-75%) and excellent score 16-20 (i.e. 80-100%). Table I shows that 21 (48.84%) male and 28 (45.9%) female students obtained good scores. Likewise, 39 (51.32%) Hindu and 10 (35.71%) Muslim students obtained good scores. The difference between the average scores of male and female students, as well as that of Hindu and Muslim students were not significant statistically.

This Table also shows the knowledge of personal hygiene among primary school children. A score = 0 corresponded to “don’t know / incorrect knowledge”; and a score = 1, to “correct knowledge”. Therefore, overall, the maximum and minimum possible scores were 10 and 0, respectively. Poor score was considered to be a score < 4 (i.e. < 40%), and other scores categorized were good score 4-6 (i.e. 40-60%) and very good / excellent score 7-10 (i.e. 70-100%). It was found that 28 (65.12%) male and 50 (81.97%) female students obtained good scores. The average score obtained by the female students was significantly higher than that of the male students ( $p < 0.05$ ). Equal proportion (75% each) of Hindu (57) and Muslim (21) students obtained good scores. There was no significant difference between the average scores of Hindu and Muslim students.

Table II shows that the proportion of primary school children having correct practices regarding combing hair, studying under adequate light, brushing teeth, washing hands before eating and trimming nails was significantly lower compared to the proportion of primary school children having correct knowledge on each of these indicators (48.08% vs. 74.04%, 8.65% vs. 40.38%, 50% vs. 65.38%, 84.62% vs. 96.15%, and 76.92% vs. 98.08%, respectively). Regarding wearing shoes, the proportion of primary school children having correct practice was significantly higher than the proportion of primary school children having correct knowledge (55.77% vs. 25%).

The proportions of primary school children having misconceptions regarding studying under adequate light (59.62% or 62 students), wearing shoes (75% or 78 students) and wearing clean clothes (85.58% or 89 students) were much more than the proportions of primary school children having misconceptions on other indicators of personal hygiene (ranged from 0.96% to 13.46%, or 1 to 14 students) (Tab. III).

Almost three-fourth of the primary school children (74.04% or 77 students) were suffering from one or more morbidities related to poor personal hygiene. The most common morbidity reported by them was diarrhoea (56.73% or 59 students), followed by fever with or without cough / cold (54.81% or 57 students), passage of worms in stool (45.19% or 47 students), head lice (40.38% or 42 students), scabies (39.42% or 41 students), dental caries (9.62% or 10 students) and multiple boils (7.69% or 8 students) (Tab. IV).

Among 71 primary school children with illiterate mothers, 18 students (25.35%) obtained poor score for practices of personal hygiene, whereas 42 students (59.15%) obtained good score and 11 students (15.50%) obtained

Tab. II. Distribution of students according to correct practice and correct knowledge of personal hygiene (n = 104).

Indicators of personal hygiene*	Correct practice (n = 104)	Correct knowledge (n = 104)	Z (Significance, p-value)
Combing hair	50 (48.08)	77 (74.04)	-4.21 (Significant, $p < 0.01$ )
Studying under adequate light	9 (8.65)	42 (40.38)	-5.22 (Significant, $p < 0.01$ )
Brushing teeth	52 (50.00)	68 (65.38)	-2.2 (Significant, $p < 0.05$ )
Washing mouth after eating	64 (61.54)	75 (72.12)	-1.59 (Not significant, $p > 0.05$ )
Washing hands before eating	88 (84.62)	100 (96.15)	-2.76 (Significant, $p < 0.05$ )
Washing hands after visiting toilet	98 (94.23)	103 (99.04)	-1.87 (Not significant, $p > 0.05$ )
Trimming nails	80 (76.92)	102 (98.08)	-4.52 (Significant, $p < 0.01$ )
Taking bath daily	44 (42.31)	47 (45.19)	-0.41 (Not significant, $p > 0.05$ )
Wearing shoes	58 (55.77)	26 (25.00)	4.43 (Significant, $p < 0.01$ )
Wearing clean clothes	13 (12.50)	15 (14.42)	-0.4 (Not significant, $p > 0.05$ )

Figures in the parentheses indicate percentages; \* Multiple responses.

**Tab. III.** Distribution of students having misconceptions regarding personal hygiene (n = 104).

Misconceptions among students regarding*	Number (%)
Combing hair	1 (0.96)
Studying under adequate light	62 (59.62)
Brushing teeth	14 (13.46)
Washing mouth after eating	3 (2.88)
Washing hands before eating	4 (3.85)
Washing hands after visiting toilet	1 (0.96)
Trimming nails	2 (1.92)
Taking bath daily	14 (13.46)
Wearing shoes	78 (75.00)
Wearing clean clothes	89 (85.58)

\* Multiple responses.

**Tab. IV.** Distribution of students according to morbidities related to poor personal hygiene (n = 104).

Morbidities related to poor personal hygiene* (history over last 15 days)	Number (%)
Fever with or without cough / cold	57 (54.81)
Diarrhoea	59 (56.73)
Passage of worms in stool	47 (45.19)
Head lice	42 (40.38)
Dental caries	10 (9.62)
Scabies	41 (39.42)
Multiple boils	8 (7.69)

\* Multiple responses.

very good score. Among 33 primary school children with maternal education primary and above, only one student obtained poor score, whereas 7 students (21.21%) obtained good score and 16 students (48.48%) obtained very good score. Nine primary school children obtained excellent score and their mothers had middle school education and above. Statistically significant association was observed between practices of personal hygiene among primary school children and literacy status of their mother ( $p < 0.001$ ) (Tab. V).

## Discussion

The children of today will be the adults of tomorrow. By focusing on children today, by giving them tools and knowledge to change behavior, future generations can be stronger and healthier [1]. In the present study, it has been observed that the female students obtained significantly higher average score than the male students regarding the knowledge of personal hygiene.

This study shows that 98 (94.23%) primary school children washed their hands after visiting toilet and 88 (84.62%) washed their hands before eating. Also, 50 (48.08%) primary school children combed their hair, 52 (50%) brushed their teeth, 80 (76.92%) trimmed their nails, 44 (42.31%) took daily bath, 58 (55.77%) wore shoes and only 13 (12.5%) wore clean clothes. These observations clearly indicate that hygienic practices for

all the indicators of personal hygiene were not adequate among the study population. A study conducted in Philippines (1996) indicated that 71.4% school children washed their hands after using toilet and 75.9% washed their hands before eating. Also, 65.2% school children took daily bath and 63.8% wore slippers and shoes most of the time. Only 39.5% regularly trimmed their nails [3]. A study conducted by Dongre et al. (2006) among tribal school children in India reported that only 27.6% students (6-14 years) had clean and combed hair, 29.7% had clean and cut nails, 42.8% wore clean clothes and 33.8% had clean teeth before implementing the school health education program [4]. Another study by Dongre et al. (2007) in rural India documented that 63.6% school going children (6-14 years) had practice of hand washing with soap after defecation and 67.8% had clean and cut nails before initiating hygiene education [5]. A study done in rural Ethiopia by Vivas et al. (2010) shows that 99% of primary school children (mean age 10.8 years) washed their hands before meals, whereas only 15% washed their hands after defecation on the day prior to the interview [6]. Therefore, the present study and similar studies from the developing countries show that the practices of personal hygiene are not satisfactory among primary school children in the developing world.

The present study also shows that there was a wide gap between practice and knowledge regarding most of the indicators of personal hygiene. This finding corroborates with the study done in Philippines (1996) [3], as well as with a study by Oyibo (2012) done in Nigeria among school children aged 6-14 years [7]. It is quite expected that a lesser percentage of students having correct knowledge will be able to translate their knowledge into practice. This has been observed clearly in the present study, and this observation supports the principle of health education that knowledge does not necessarily lead to practice. In addition, lack of proper resources, i.e. soap and water, as well as inadequate sanitation facilities in a slum community with low socio-economic condition may negatively affect personal hygiene practices. Moreover, it has been observed that a good fraction of students have adopted to the right practices regarding some of the indicators, e.g. wearing shoes, without having correct knowledge on it. Even, misconceptions regarding the maintenance of personal hygiene were not uncommon among the primary school children, as observed in this study. This indicates that enhancement of knowledge is necessary, and the depth to which the knowledge is imparted to the students is not adequate. This calls for immediate attention of measures so that the knowledge is enhanced, as well the depth of knowledge is increased among primary school children. In this regard, the school teachers, parents and other family members could play a vital role. Even, children can also be the agents of change subsequently by spreading what they have learned in school to their family and community members. In this connection, the Total Sanitation Campaign (TSC) as launched by Government of India in 1999 worth acknowledgement. The TSC gave emphasis on personal



**Tab. V.** Distribution of students according to practice of personal hygiene and literacy status of mother (n = 104).

Practice of personal hygiene (score)	Literacy status of mother			Total
	Illiterate <sup>a</sup>	Primary <sup>b</sup>	Middle <sup>c</sup> and above	
Poor (< 8)	18 (25.35)	1 (5.55)	-	19 (18.27)
Good (8-12)	42 (59.15)	5 (27.78)	2 (13.33)	49 (47.12)
Very good (13-15)	11 (15.50)	12 (66.67)	4 (26.67)	27 (25.96)
Excellent (16-20)	-	-	9 (60.00)	9 (8.65)
Total	71 (100.00)	18 (100.00)	15 (100.00)	104 (100.00)

Figures in the parentheses indicate percentages; <sup>a</sup> *Illiterate*: Those who cannot read or write; <sup>b</sup> *Primary*: Grade I to IV. <sup>c</sup> *Middle*: Grade V to VIII;  $\chi^2 = 36.7$ , d.f. = 2,  $p < 0.001$ . Chi-square test was applied after classifying literacy status of mother as illiterate and literate (with education primary and above), and practice of personal hygiene as poor, good and very good / excellent.

hygiene, home sanitation, safe water, garbage disposal and wastewater disposal. It emphasized more on health education, human resource development, and capacity development activities to increase awareness and sanitation demand [1]. The TSC also laid strong focus on school sanitation and hygiene promotion. Among the main objectives of the TSC, accelerating sanitation coverage and promoting hygiene behavior among students and teachers are worth mentioning [8].

In this study, almost 75% of the primary school children were suffering from one or more morbidities related to poor personal hygiene. The most common morbidity reported by them was diarrhoea (56.73%), followed by fever with or without cough / cold (54.81%), passage of worms in stool (45.19%), head lice (40.38%), scabies (39.42%), dental caries (9.62%) and multiple boils (7.69%). These observations are quite similar to that of the study by Dongre et al. (2006) among tribal school children in India [4], where 56.6% students had diarrhoea, fever and upper RTI (respiratory tract infections), followed by head lice (42.8%), scabies (36.6%), multiple boils (8.9%), dental caries (8.3%) and history of worm infestation (28.9%) before implementing the school health education program.

In the present study, more than half of the primary school children (59.15%) with illiterate mothers obtained good score, followed by poor score (25.35%). Whereas, almost half of the primary school children (48.48%) with maternal education primary and above obtained very good score. Nine primary school children (8.65%) obtained excellent score and their mothers had middle school education and above. Only one primary school children (out of 33) with maternal education primary and above obtained poor score, whereas no primary school children (out of 71) with illiterate mother obtained excellent score. Statistically significant association was observed between practices of personal hygiene among primary school children and literacy status of their mother ( $p < 0.001$ ). In this connection, it can be said that maternal education can play a vital role in the practices of hygiene and health among their children. As an illiterate or uneducated mother may be less knowledgeable about teaching her children proper personal hygiene practices. So, continuing health education program directed to the parents with a special emphasis on their role to improve the health habits of their children may hold promise.

The Author acknowledges the limitations of this study and implications for future improvement. First, the sample size was small. Second, the nutritional status of the children was not studied, which might be related to the state of personal hygiene as well as related morbidities. Third, morbidity pattern of the children was assessed by history and clinical examination. No attempt was made to perform any laboratory test, e.g. stool examination for parasites to detect the presence of any parasitic infection. These aspects need to be taken care of in future.

This study was undertaken among the primary school children in a slum area of Kolkata, India. The findings of the study might not corroborate with similar studies from non-slum areas of Kolkata, as the low socio-economic condition and the compromised living situation in a slum community along with inadequate primary health care services do not allow its people to adopt proper hygienic behavior and to observe good health.

## Conclusions

It can be concluded from the present study that knowledge and practice of personal hygiene among the primary school children in a slum area of Kolkata, India is not satisfactory. Although, female students appear to be more knowledgeable than the male students. Sadly, knowledge and practice on all the indicators of personal hygiene are not commensurate and they are not equally good on all the indicators of personal hygiene among the primary school children. Even, misconceptions do exist on certain indicators of personal hygiene among the students. Students with poor hygienic practices mostly suffer from diarrhoea, fever with or without cough / cold, passage of worms in stool, head lice, scabies, dental caries and multiple boils.

Therefore, there is an immediate need for enhancement of knowledge among the primary school children, where teachers and parents can play a pivotal role. School-based health education program may be a useful effort in this regard. In this connection, the role of parent-teacher associations in all the schools should be emphasized. Maternal education appears to have a direct relation with the practices of personal hygiene among the primary school children. In this regard, not only the formal education, but continuing health education program of the parents by health workers, television and other me-

dias may also hold promise. Not only that, infrastructural development for proper maintenance of personal hygiene along with financial upliftment of the parents may go a long way so far educating the students and providing them with necessary resources and facilities are concerned. This in turn will help the students in adopting proper hygienic behavior. Government–NGO (non-governmental organizations) collaboration may also prove to be effective in achieving these goals.

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# Frequency and profile of induced abortions: hospital based study in tertiary hospitals in Egypt

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## Key words

Induced abortion • Tertiary hospitals • Egypt

## Summary

**Objectives.** To determine the frequency and profile of induced abortions among hospitalized cases of abortions in three tertiary hospitals in Egypt.

**Methods.** A total of 517 consecutive cases of abortions with complete records were enrolled from three tertiary hospitals in Egypt: two hospitals in Cairo and one hospital in Alexandria. A data extraction sheet was designed to extract the required information from the records. It included: File No., Age, marital status, occupation, parity, number of children, previous abortion, history of contraception, trial of induction for this abortion and management of abortion in the hospital. The World Health Organization (WHO) criteria of categorizing the abortion as possible, probable or certainly induced abortion was used for classification of abortion cases.

**Results.** The proportion of classified induced abortions (certainly, probably and possibly induced abortions) was 30.6% in the total sample, being higher in Alexandria hospital (60.9%) compared to 14 and 19% in the other two hospitals respectively. Using the multiple logistic regression, the following factors were found independently related to induced abortions: Alexandria hospital (as proxy for residence), age  $\geq 30$  years and having more than 2 children.

**Conclusion.** The current study revealed that about one third of hospitalized cases of abortion can be suspected of being induced. Induced abortion may be linked to elder age, higher number of children in the family and probably have geographical variation in Egypt.

## Introduction

The conditions under which abortion is legally permitted are different in different countries [1]. It is estimated that almost 40% of pregnancies over the world are unplanned [2]. However, in Islamic countries, this is completely forbidden except for medical reasons. Where induced abortion is illegal and largely inaccessible, little information is available on abortion practices outside the legal framework, putting women at the edge of unsafe abortion. Unsafe abortion refers to the termination of an unintended pregnancy either by persons lacking the necessary skills or in an environment lacking the minimal medical standards, or both [3]. With such legal, ethical and religious considerations that hinder reporting, occurrence tends to be under-reported in surveys, and unreported or under-reported in hospital records. Only the "tip of the iceberg" is, therefore, visible in the number of deaths and the number of women who suffer severe trauma, or who have an infection or severe blood loss and seek medical care [4].

During rapid transition from high to low fertility, as has been witnessed in Egypt, contraceptive services are often unable to meet the growing demand of couples for fertility regulation, resulting in an increased number of unplanned pregnancies, some of which are terminated

by induced abortion. Also, where less effective family planning methods are commonly used, unplanned pregnancies and, consequently, abortions are likely to occur [4]. This puts additional sight to the importance of the issue of induced abortions nowadays.

The aim of this study is to determine the frequency and profile of induced abortions among hospitalized cases of abortions in three tertiary hospitals in Egypt.

## Subjects and methods

The current study was carried out in three tertiary hospitals in Egypt: one university hospital (A) and one specialized tertiary hospital in Cairo (B); while the third hospital is a university hospital in Alexandria (C). The three hospitals were selected as they are the biggest tertiary and reference hospitals in the largest two cities in Egypt: Cairo and Alexandria.

## SAMPLE SIZE

A sample size with 95% confidence interval was calculated to be at least 350 hospitalized subjects with abortion to detect proportion of induced abortions of  $65\% \pm 5\%$  according to previous Egyptian study [5]. The same sample size was able to detect a proportion of  $35\% \pm 5\%$  according to more recent published data in

Tab. I. Characteristics of the study group.

	University Hospital in Cairo (A)	Tertiary Hospital in Cairo (B)	University Hospital in Alexandria (C)	Total
No. enrolled	151	205	161	517
Age (M ± SD)	27.6 ± 6.5	27.55 ± 6.3	29.5 ± 5.6*	28.18 ± 6.2
Working women [No.(%)]	8 (5.3)	9 (4.4)	60 (37.3)**	77 (14.9)
No. Children [No. (%)]				
0	58 (38.4)	66 (32.2)	4 (2.5)	128 (24.8)
1-2	62 (41.1)	90 (43.9)	96 (59.6)	248 (48)
≥ 3	31 (20.5)	49 (23.9)	61 (37.9)	141 (27.3)

\*p < 0.05 vs. Hospital A & B; \*\* p < 0.001.

Iran (a country with comparable demographic characteristics like Egypt) [6].

The method of data collection was retrospective medical record review. A total of 517 consecutive cases of abortions with complete records were enrolled from the three selected hospitals. A data extraction sheet was designed to extract the required information from the records. It included: File No., Age, marital status, occupation, parity, number of children, previous abortion, history of contraception, trial of induction for this abortion and management of abortion in the hospital. When any of the required information was missing in the record, the record was not selected. All field investigators were selected with medical background (some doctors and some high institute nurses). They were trained on the extraction sheet. Collected data were randomly re-checked by independent supervisors.

Data from the medical records were extracted anonymously and used only for the current research, The medical record number was used only for validation of data. The following World Health Organization criteria for distinguishing induced from spontaneous abortion were used [7]:

- Certainly induced abortion: when the woman herself provides this information, or when such information is provided by a health worker or a relative (in the case of the woman dying), or when there is evidence of trauma or of a foreign body in the genital tract.
- Probably induced abortion: when the woman has signs of abortion accompanied by sepsis or peritonitis, and the woman states that the pregnancy was unplanned (she was either using contraception during the cycle of conception or she was not using contraception because of reasons other than desired pregnancy).
- Possibly induced abortion: if only one of the “probably” induced conditions listed above is present.
- Spontaneous abortion: if none of the conditions listed above is present, or if the woman states that the pregnancy was planned and desired.

#### DATA ANALYSIS

Data were coded and analyzed using the SPSS program. Qualitative data were presented in frequency and percentage while quantitative data were presented in mean and standard deviation. Logistic regression was used to identify independent factors related to induced abor-

tions. Odds ratio and 95% confidence intervals were used to quantify the risk.

## Results

A total of 517 abortion records were selected for this study from the three hospitals. Alexandria hospital (C) had cases with higher mean age and higher percentage of working women than the other 2 hospitals (Tab. I). As shown in Table II, the percentage of classified induced abortions (certainly, probably and possibly induced abortions) was 60.9% in C compared to 14% & 19% in the other two hospitals respectively. No cases with certainly induced abortion were reported in the A and B and 9 cases were classified as certainly induced abortions in C. Among the nine cases classified as certainly induced abortions, 4 of them were induced by a midwife and uncontrolled bleeding was the reason of hospitalization in seven cases. After hospital admission, 6 cases were diagnosed with incomplete abortion and 2 cases with threatened abortion and only one case with septic abortion (Tab. III). Using the multiple logistic regression, the following factors were found independently related to induced abortions: Alexandria hospital (as proxy for residence), age ≥ 30 years and having more than 2 children (Tab. IV)

## Discussion

It is estimated that million of pregnancies are voluntarily terminated each year, almost half of them outside the legal national system where the abortions are often performed by unskilled providers or in unhygienic conditions, or both [8].

In studying induced & unsafe abortions, especially in a country like Egypt where such practice is illegal, it is expected that patients will deny induced abortions. Thus, the health care facility is the most logical, cost-effective and convenient place to conduct the research where women with complications are treated. For this reason, the majority of abortion studies have been hospital-based and it is likely that most future studies will be conducted in hospitals as well [9].

The current study showed that the personal characteristics of abortions admitted in hospitals differs from one area to another. In Table I, abortion cases in Alexandria

Tab. II. Frequency of induced abortions in the studied hospitals.

	University Hospital in Cairo (A) No. (%)	Tertiary Hospital in Cairo (B) No. (%)	University Hospital in Alexandria (C) No. (%)	Total No. (%)
Certainly induced	0 (0)	0 (0)	9 (5.6)	9 (1.7)
Probably induced	0 (0)	1 (0.5)	2 (1.2)	3 (0.6)
Possibly induced	21 (13.9)	38 (18.5)	87 (54)	146 (28.2)
Spontaneous abortion	130 (86.1)	166 (81)	63 (39.1)	359 (69.4)

hospital had higher mean age and higher prevalence of working women.

In most of Islamic countries as well in other countries, where induced abortions are illegal, such induced abortions are often under-reported. The WHO classification of abortion was developed to overcome such problem and was used in this study to classify abortions whether induced or not [7]. The present study revealed that classified induced abortions (certainly, probable and possible induced abortions) accounted for almost 30% of the studied cases (Tab. II). A former study, carried out in Egypt many years ago, reported higher prevalence of almost 65% [5]. However, the current study was carried out in tertiary hospitals in the biggest two cities: Cairo and Alexandria in contrast with the former study that took a sample of public hospitals across the different cities. A study carried out in Iran, a country with comparable cultural and religious background to Egypt, revealed that 12% of hospitalized abortions reported that they were illegally induced although about 35% of these pregnancies were not planned which may infer that such abortions percentage is underestimated [6]. Earlier studies showed percentage of induced abortions among all hospitalized abortions ranging from 15% [10] to more than 50% [11] which points to wide variation among different countries.

Table III showed that among the certainly induced reported abortions, 4 cases (44%) were carried out by a midwife. In Pakistan, midwives also were responsible for 43.8% of induced abortions [12]. In contrast, most cases of induced abortion in Latin America are medication induced [13, 14]. This may be evidently linked to difference in culture and sexual behavior that pose women in some countries like Brazil to earlier and repeated experience. Bleeding was the main cause of hospitalization of certainly induced abortions and all of the 9 cases categorized as certainly induced abortions were given hospital diagnosis other than induced abortion (Tab. III).

The current study showed that elder age ( $\geq 30$  ys), having more than 2 children, and Alexandria hospital (C) were independent predictors of induced abortions (Tab. IV). Huntington and his colleagues, in their previous study in Egypt concluded a similar finding regarding age relation to the induced abortions where induced abortions had higher mean age than cases with spontaneous abortions [8]. Other studies reported younger age as a risk factor for induced abortions [13] but this may be interpreted by the difference in sexual behavior in the different countries. In some countries where sexual behavior before marriage at younger age is common, un-

Tab. III. Profile of the reported (certainly) induced abortions.

	NO. (%) n = 9
Method used	
Self induced with medication	1 (11.1)
Self induced with unspecified method	4 (44.4)
Midwife	4 (44.4)
Reason of hospitalization	
Bleeding	7 (77.8)
Non-specific	2 (22.2)
Hospital Diagnosis	
Threatened abortion	2 (22.2)
Incomplete abortion	6 (66.7)
Septic abortion	1 (11.1)
Hospital management	
D&C/ suction & evacuation	7 (77.8)
Medical management	2 (22.2)

wanted pregnancies may be common and hence induced abortions may be prominent at younger age. In contrast, where sexual behavior before marriage is not common, as in our country, unwanted pregnancies may be linked to failure or underutilization of contraceptive methods which occur later in the marriage history.

As shown in Table IV, number of children (more than 2) was identified as an independent risk factor for induced abortion. Higher number of children can be regarded as determinant of unwanted future pregnancy that in turn is linked to induced abortion. In Egypt, More than half of women in reproductive age group want to limit their family size to only two children [15]. This agrees with many studies that observed higher risk of induced abortions in presence of more children in the family [12, 16, 17]. The current study revealed an interesting finding, where classified induced abortions were significantly more frequent in Hospital C than the other two hospitals. All three hospitals have the same scope and level of health-care service. Yet, Hospital C is located in different city with probably different referred population. Thus, Hospital C was regarded as proxy for the residence. Induced abortions have shown relation to geographic variation within the same country [18, 19]. This can be explained by socio-cultural disparities within same country that have impact on sexual practices as well perception of fertility.

The current study highlighted the potential burden of induced abortion; a masked health problem in our country; and its possible determinants. The study identified some predictable determinants like elder age and

Tab. IV. Factors related to induced abortions.

	Induced abortions No. (%)	Spontaneous abortions No. (%)	OR (95% CI)*
<b>Hospital</b>			
A	21 (13.3)	130 (36.2)	1
B	39 (24.7)	166 (46.2)	1.5 (0.8-2.9)
C	98 (62)	63 (17.5)	11.1 (5.8-21)
Working women	27 (17.1)	50 (13.9)	1.3 (0.8-2.1)
Age $\geq 30$	92 (60.1)	108 (30.9)	2.3 (1.4-3.7)
No. children > 2	85 (53.8)	56 (15.6)	4.6 (2.8-7.7)

\* Using logistic regression.

high number of children in the family, yet it pointed a possible importance of geographical variation of such practice within Egypt. This would call for researches that study such geographical distribution of induced abortions.

#### LIMITATION OF THE STUDY

This study was conducted on cases of abortion admitted to tertiary hospitals and the method of collection of data

was record review. Data extracted from record review are limited to those provided in the record. Accordingly important potential risk factors like education, income and other social factors were missed from such study as they were not included in the medical record. Study of induced abortion in a country like Egypt represents a challenge as subjects will often deny such practice, making interviewing of subjects difficult and threaten validity and reliability of the tool.

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# Testicular-self examination among Nigerian adolescent secondary school boys: knowledge, attitudes and practices

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## Key words

Adolescents • Attitudes • Knowledge • Testicular self examination • Students

## Summary

**Background.** Testicular-self examination (TSE) is a cheap and easy-to-perform procedure for early detection of testicular cancer but data on this subject is lacking in Nigeria, particularly among male adolescents.

**Objective.** To assess the knowledge, attitudes and practices of testicular-self examination among secondary school boys.

**Methods.** Knowledge, attitudes and practices in relation to TSE were assessed, using anonymous structured self-administered questionnaires in a sample of 540 secondary school boys aged between 15 and 20 years.

**Results.** Nearly all (98.7%) the male students had never heard of TSE and had hardly practiced TSE. Of the 7 students who admitted

examining their testicles, none did so at the recommended level (10 or more times per year) and did not follow the standard procedure for TSE. Nearly half (47.2%) of the participants had a positive intention to start performing TSE regularly after hearing of TSE (through the questionnaire and subsequent teaching on the subject).

**Conclusions.** The level of knowledge, practice and the rating of the importance of TSE are all very low among adolescent secondary school boys in Benin City, suggesting that these students are unaware of the value of this personal health surveillance tool. The students demonstrated a positive intention to start performing TSE regularly after hearing of TSE (through the questionnaire and subsequent teaching on the subject).

## Introduction

Testicular-self examination (TSE) refers to the procedure by which a man checks the appearance as well as the consistency of his testicles. It is a simple, painless procedure, easy-to-learn and requiring about three minutes to complete. It is an important clinical tool for early detection of testicular cancer (TC). TSE offers adolescent boys and young men the opportunity to routinely and systematically examine their testicles. In this regard, it has been recommended that young men (between the ages of 15 and 35 years) should practice TSE every month. This recommendation is buttressed by the fact that nine out of every ten TC is first discovered by the individual himself [1]. Although testicular cancer is uncommon among teenagers, it has been documented as the most common cancer in males between the age of 15 and 34 years [2]. To ensure early detection, the teenager has to look for any hard lumps or smooth rounded bumps or any change in size, shape and consistency of the testes. Early detection and treatment results in cure, underscoring the important role TSE can play [3]. The earliest detectable symptom of TC is a small, hard and usually painless lump in the testes [3]. The principal risk factor for TC is cryptorchidism and this risk is as high as 30-40% when compared to males with normally descended testicles [4]. In this context, therefore, TSE on

a routine basis is particularly important for males with cryptorchidism. Other risk factors for testicular cancer are a positive history of a family member who has had this cancer or a previous testicular cancer.

In developed countries, several studies have reported a very poor knowledge as well as a low rating of the importance of this screening tool (TSE) among young male individuals. For instance, in two separate studies, one in the US and the other in Europe, only 10.3% and 3.0% of males performed TSE at levels consistent with current recommendations [5, 6]. If at risk age group with high levels of education are not carrying out the recommendation, the level of compliance in less educated population, like Nigeria and other developing countries, will be next to zero. Although most adolescent and young women know that breast-self examination is a good health habit, most teenage boys and young men do not know that TSE is a self-health surveillance procedure that they need to establish as a life-time habit beginning from the period adolescence. For instance, reports from Nigeria indicated a high level of awareness and knowledge with regard to breast-self examination [7, 8]. With regard to the subject of TSE, data on adolescent males is scanty in developed countries, and more so, in developing countries. A review of the literature did not reveal any study on the subject among Nigerian adolescent secondary schoolboys. This scenario is further confirmed by the

report of Carlin [9] in which she stated that in a review of the literature, physical assessment texts made no mention of TSE, even though the Authors encouraged the practice of breast self-examination for adolescent girls and young women. Although the worldwide increasing incidence of TC has been recognized, the reports of various surveys revealed that knowledge, awareness and performance of TSE among adolescent and young adult males remain poor [10, 11].

The purpose of the present study was to assess the knowledge, attitudes and practices of TSE among adolescent Nigerian secondary school boys in Benin City. The data obtained might serve as a starting point in arousing public interest on TC and ultimately, encouraging the practice of TSE among adolescent Nigerian boys.

## Materials and methods

This descriptive cross-sectional study, was conducted in one of the public senior secondary schools for boys' only in Oredo Local Government Area (OLGA), Edo State, Nigeria. In this LGA, there are nine public secondary schools comprising 3 co-educational, 4 all girls and 2 all boys [12]. One out of the two all-boys' secondary schools, was randomly selected by ballot. In this selected school, the total population of students between the age of 15 and 20 years was 594 and this constituted the study sample. No sampling was performed since the survey was designed to include all the students in this school who were between the age of 15 and 20 years. During data collection, the students were informed about the relevance of the study and the need to accurately fill the questionnaire without including their names and that their participation was voluntary. Permission to conduct the survey was obtained from the school administrators. Data was collected between October and November, 2011, using a structured questionnaire designed by the Authors. The questionnaire was pre-tested on 30 male students of the same age group in the other all boys' school within the same LGA. The class teacher assisted in identifying the students within the relevant age group from the class register. The questionnaire was divided into two parts: the first part sought information on socio-demographic data, such as age of participants, educational status of father and mother, occupation of father and mother, religion and state of origin. The socio-economic status of the parents was determined using the classification suggested by Ogunlesi et al [13]. This was analyzed via combining the highest educational attainment, occupation and income of the parents (based on the mean income of each educational qualification and occupation). In this Social Classification System, classes I and II represent high social class, class III represents middle social class while classes IV and V represent low social class. In this way, the adolescent girls were divided into high, middle and low socio-economic groups. The second part of the questionnaire assessed the knowledge, attitudes and practices of TSE among the students. Knowledge about TSE was assessed based on

questions concerning steps in the performance of TSE, frequency of performance, and what to look out for during TSE. The students' rating of the importance of TSE was also assessed. Data were obtained on whether or not the student practice TSE and how frequently he did so. After the students have completed the questionnaire, we explained to them how to perform a TSE. The best time to perform TSE is during or after a warm bath because the scrotum is most relaxed at this time and this makes it easier to examine the testicles.

The data was analyzed using the SPSS (Statistical Package for Social Sciences), version 12.0. Where applicable and appropriate, descriptive statistics such as frequencies, means, ratios, standard deviations, confidence intervals, percentages were used to describe all the variables.

## Results

Out of a total population of 594 male students, 571(96.1%) participated but 31 questionnaires were incompletely filled and were rejected, leaving 540 for data analysis. The mean age of the students was  $16.8 \pm 1.7$  years (95% Confidence Interval, CI = 16.6-16.9). As shown in Table I, slightly above half of the students (52.6%) came from families in the low socio-economic status and over three-quarter of the students were from Christian families. Only seven (1.3%) of the 540 have heard about TSE and the information was obtained from friends and peers (Table II). None of the students received information on TSE from a health-care provider. Of the seven who admitted to have heard about TSE and practiced it, none has practiced it in the last three months. As depicted in Table II, over half of the students could not rate the importance of TSE while nearly one-third of the students rated the importance of TSE as very low. As shown in Table II, nearly half (47.2%) of the students had a positive intention to start performing TSE regularly after hearing of TSE (through the questionnaire). None of the students was aware that testicular cancer can occur among people who are less than 20 years old.

## Discussion

Data from the present study indicated that regarding TSE, adolescent male students were grossly uninformed as only 1.3% of them had heard and practiced TSE (not at the recommended level). An extensive search of the literature did not reveal any Nigerian study on adolescent school boys for comparison. However, a study among adults (aged 18 to 50 years old) in three tertiary institutions in Port Harcourt revealed a similar poor knowledge and attitude concerning the subject [11]. The finding of low knowledge with regard to TSE is not surprising, given that a similar low level of awareness has been separately reported in several studies conducted in developed countries with highly literate populations. For



Tab. I. Socio-demographic characteristics of the participants.

Age	Group (years)	Number	Percent
15-17	387	71.7	
18-20	153	28.3	
<b>Socioeconomic status (SES)</b>			
High	73	13.5	
Middle	183	33.9	
Low	284	52.6	
<b>Family religion</b>			
Christian	429	79.4	
Muslim	74	13.7	
Traditional religion	37	6.9	
<b>State of origin</b>			
Edo	415	76.9	
Other states	125	23.1	

instance, among young German, Icelandic and Dutch men the practice prevalence rates of regular TSE were 3.0%, 2.0% and 2.0% respectively [5, 14]. This low level of practice of TSE was further highlighted in a study in the United States in which only 29.0% of male Paediatric Resident Doctors performed TSE regularly [15]. A comparative study of British and Zimbabwean undergraduates revealed that knowledge of TSE was low in both groups of participants [16]. Another study in Turkey revealed poor knowledge of TSE among college male adolescents [17]. All these studies consistently pointed to a low level of knowledge and practice with regard to TSE among adolescent male students. This scenario about knowledge and practice of TSE might be explained by lack of awareness by adolescent males that testicular cancer can occur in them and that TSE is a potential screening tool for early detection of testicular cancer and hence, treatment and cure. Another explanation might be that the clinicians themselves do not instruct their male patients about TSE and encourage them to undertake regular monthly examination [5]. This view is reinforced by the report of a study in which only 17.5% of physicians surveyed taught TSE to adolescent male patients on a routine basis [18]. In that study, 82.0% of the physicians stated they were either not familiar with the technique of TSE or had not thought about it. This situation is further reflected in our finding that none of the seven participants who have heard about TSE did so from healthcare providers. On the other hand, the low level of knowledge and practice observed in the present study might be explained by cultural factors. Generally speaking, it is not in our culture to discuss freely issues involving the genitals in the public. The students may have been shy to admit that they do examine their testicles. Given the observed increasing incidence of testicular cancer among the primary at risk age group of between 15 and 34 years, there is an urgent need to educate male adolescents on the subject of TSE, leading to promotion of personal health surveillance via early testicular cancer detection and treatment with the ultimate aim of saving lives [10].

Tab. II. Knowledge, attitudes and practices of testicular-self examination (TSE) among 540 participants.

Questions and answers	Number	Percent
<b>Have you heard about TSE?</b>		
Yes	7	1.3
No	533	98.7
<b>What tool (s) do you need to perform it?</b>		
None	282	52.2
Mirror	21	3.9
I do not know	237	43.9
<b>The two steps involved in TSE are inspection and feeling:</b>		
Yes	93	17.2
No	133	24.6
I do not know	314	58.2
<b>How often should TSE be performed?</b>		
Once every month	38	7.0
Once every 3 months	70	13.0
<b>Once every 6 months 99 18.3</b>		
Once every year	57	10.6
I do not know	276	51.1
<b>Is TSE important?</b>		
Yes	88	16.3
No	147	27.2
I do not know	305	56.5
<b>If important, how will you rate it (0-10)? (n = 88)</b>		
0-3	50	56.8
4-6	23	26.1
7-10	15	17.1
<b>Having heard of TSE through this questionnaire, do you intend to practice TSE regularly?</b>		
Yes (Positive)	255	47.2
No (Negative)	116	21.5
Undecided (neutral)	169	31.3
<b>The risk of testicular cancer is highest among those aged:</b>		
15-35 years	3	0.6
Above 35 years	537	99.4

As in previous studies [5], a low rating of the importance of TSE was observed in the present study. The implication of the low rating of the importance of TSE is that even when the adolescent males become informed on the subject they may not practice it (TSE). Although in the present study, nearly half (47.2%) of the students indicated a positive intention to practice TSE regularly after hearing about it, this finding should be taken with caution considering the possibility that the students may want to please the Authors by indicating a positive intention. On the other hand, a similar finding of a positive intention to start practicing TSE regularly after hearing about it has been observed in another study. This might be a reflection of the readiness of these male adolescents to accept and practice TSE regularly, suggesting that educating the students on the subject has a high potential to succeed. Data from the present study indicated that all the students were unaware that testicular cancer can occur in individuals below twenty years of age. A similar finding

has been reported in previous studies [6,19]. This is worrisome because unawareness of the existence of testicular cancer resulted in the low rating of the importance of TSE as observed in this study. Testicular cancer is a fast-growing tumour and the prognosis depends largely on the time of starting effective therapy.

In conclusion, the level of knowledge, practice and the rating of the importance of TSE are all very low among

adolescent secondary school boys in Benin City, suggesting that these students are unaware of the value of this personal health surveillance tool. The students demonstrated a positive intention to start performing TSE regularly after hearing of TSE (through the questionnaire and subsequent teaching on the subject). Health education, using video presentations in schools and promotion of regular and accurate TSE is suggested.

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# Sequence based typing of *Legionella pneumophila* sg 1 isolated in nosocomial acquired infections in Apulia, Southern Italy

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## Key words

*Legionella pneumophila* sg 1 • Sequence based typing • Nosocomial acquired infections

## Summary

**Objective.** The present report aims to molecularly characterize seven clinical *L. pneumophila* (*L. pn.*) sg 1 isolated from nosocomial acquired infections in Apulia region, using the European Working Group on Legionella Infections (EWGLI), sequence-based typing (SBT) and amplified fragment length polymorphism (AFLP) protocols and to compare the identified sequence types (STs) with those available in the EWGLI database.

**Methods.** In the period, January 2000 - December 2012, 151 cases (136 of community and 15 of nosocomial origin) of Legionnaires' disease were notified to the Regional Center for Epidemiology. With regard to nosocomial cases, 8 were confirmed by the isolation of *Legionella* spp. from respiratory secretions. These clinical isolates were characterized by amplified fragment length

polymorphism (AFLP) and sequence-based typing (SBT), using the EWGLI standardized protocol.

**Results.** The clinical isolates belong to ST42, ST23 and ST1. The AFLP confirms the SBT results. Comparing the STs herein detected with those already in the EWGLI SBT database, the 3 STs are frequent in other European countries.

**Conclusions.** The molecular analysis demonstrates that the 3 STs are the most frequent in Italy and in Europe, supporting the hypothesis that some specific *L. pn.* sg 1 clones have gained widespread dissemination probably due to a common ecological niche. Further researches are required to investigate the potential changing incidence of STs and the fitness of emerging strains or clonal groups in environmental strains.

Legionnaires' disease (LD) is a form of pneumonia with no clinical features that clearly distinguish it from other types of pneumonia. Since the transmission occurs via inhalation of aerosols contaminated by *Legionella* spp., the frequent sources of infection are hot water systems, cooling towers and other water disseminators [1, 2]. At the same time, the problem is particularly important in hospital, where medical equipment can also be a potential source of infection (endoscopes, devices for artificial respiration and oxygen therapy, dental devices, etc) [3-5].

*Legionella pneumophila* (*L. pn.*) is the aetiological agent of approximately 90% of Legionellosis cases, and *L. pn.* serogroup 1 (sg 1) is the predominant one [6, 7]. The characterization of clinical isolates by molecular typing methods is essential for epidemiological investigations. The European Working Group on Legionella Infections (EWGLI) recently renamed European Study Group for Legionella Infections (ESGLI) has provided a description of a standardized protocol for the molecular identification of *Legionella* spp. firstly by amplified fragment length polymorphism (AFLP) [8] and more recently by sequence-based typing (SBT) [9]. In particular, SBT is a rapid and discriminatory method based on the sequence of seven loci (*flaA*, *pilE*, *asd*, *mip*, *mompS*, *proA* and *neuA*) of *L. pn.* Using the SBT protocol, the EWGLI has

built up a database allowing the assignment of the seven ordered alleles represented as a Sequence Type (ST), or allelic profile. Successively, each study participant can submit his own data in order to increase information in the database and verify the circulation of *L. pn.* genotypes in different geographic areas throughout the available *Legionella* isolates SBT map.

Apulia Region, with a land surface of 19,347 sq. km, is located in Southeastern Italy and its Regional Center for Epidemiology (OER) includes in its mission the surveillance of LD and the control of the environmental spread of *Legionella* spp. Information obtained from the environmental and clinical surveillance are maintained in a local computer database with real-time availability of all the information, allowing better programming of the necessary measures for prevention and control. At the same time, all environmental and clinical isolates of *Legionella* spp. are collected.

In the period, January 2000 - December 2012, 151 cases of LD were notified to the OER, according to the national compulsory reporting system: 136 of community and 15 of nosocomial origin. With regard to nosocomial LD cases, patient median age was 68.5 years (range 30-98), and 60% were females. Eight patients (53.3%) were confirmed by two or more diagnostic methods; overall, 80% tested positive for urinary antigen, 53.3% were

Tab. I. Clinical and molecular data of the 7 *L. pn. sg 1* isolates recovered from nosocomial acquired infections.

Isolate identification	Type of specimen, date of collection	SBT allele number (ST) (flaA, pilE, asd, mip, mompS, proA, neuA)	AFLP pattern type
Leg1u	Sputum, 11 February 2005	2,3,9,10,2,1,6 (ST23)	A
Leg2u	BA, 10 March 2004	4,7,11,3,11,12,9 (ST42)	B
Leg3u	BA, 6 October 2003	4,7,11,3,11,12,9 (ST42)	B
Leg4u	Sputum, 6 August 2002	4,7,11,3,11,12,9 (ST42)	B
Leg5u	BA, 11 September 2003	4,7,11,3,11,12,9 (ST42)	B
Leg6u	BA, 22 March 2003	4,7,11,3,11,12,9 (ST42)	B
Leg7u	Sputum, 15 March 2005	1,4,3,1,1,1,1 (ST1)	C

BA: bronchoaspirate.

confirmed by the isolation of *Legionella* spp. from respiratory secretions, 33.3% showed seroconversion and 13.3% had one single positive antibody titer. All cases diagnosed by cultural examination acquired the infection in the largest Hospital of Apulia region which is composed up of 32 separate buildings with 60 bed-operating units, for a total bed capacity of 1,400. *L. pn. sg 1* and *L. pn. sg 5* [10] were respectively isolated from seven and one patients. Since 2000, in order to contain the spread of the disease, the water system of the hospital underwent to a periodical environmental monitoring for the detection of *Legionella* spp. in water samples; moreover, additional environmental investigations are carried on when nosocomial cases are detected. According to the procedures described in the Italian Guidelines [11] treatment of disinfection (i.e., hyper-chlorination) is performed.

The present report aims to molecularly characterize the seven clinical strain of *L. pn. sg 1* isolated from nosocomial acquired infections in Apulia region, using the EWGLI SBT and AFLP protocols (version 4.2 and 1.2, respectively, <http://www.ewgli.org>), and to compare the identified sequence types with those available in the EWGLI database. *L. pneumophila* strain ATCC 33153 was included as control. The AFLP profiles were phylogenetically analyzed by the software GelCompare II (Applied Maths, Belgium) using as a cluster analysis, the Dice coefficient and the method "unweighted pair group method with averages" (UPGMA). In agreement with Fry et al. [12], the isolates with homology greater than 90% have been considered homologous strains.

The results are summarized in Table I. Our isolates can be classified into 3 distinct STs, by using the SBT method: five isolates (71.4% of all isolates) belong to the ST42, one to the ST23 (14.3%), and one to the ST1 (14.3%). The alphabetic designations (A, B and C) based on AFLP electrophoresis pattern confirm the SBT results.

The detected STs were submitted to the EWGLI SBT-database and compared to those already in. According to the EWGLI database, the ST42 profile was found ubiquitously across the Netherlands (n = 49), France (n = 29) and UK (n = 24). In Italy, a part from our 5 ST42, other

seven ST42 strains were isolated: 5 of clinical origin (1 nosocomial acquired) and two from environment.

With regard to ST1, the EWGLI database shows that its geographic distribution is mainly in France (n = 225) and UK (n = 162). In Italy, a part from our unique ST1, 26 isolates were identified: 16 were of clinical origin, of which 9 associated with nosocomial infections, and 10 were environment strains. Finally, genotype ST23 was largely present in France (n = 364) followed by the Netherlands (n = 31). In Italy, a part from our unique ST23, 19 isolates were identified: 13 were clinical strains (all community acquired or travel associated cases) and 6 environmental isolates. In addition, recently a cluster of travel-associated LD caused by ST23 in a small town located in North of Italy was documented by the Italian Institute of Health (ISS) [13].

Our molecular analysis carried out on *L. pneumophila* sg 1 clinical isolates associated with nosocomial infections, demonstrate perfectly overlapping results by both molecular methods, AFLP and SBT, as already shown by other Authors [14, 15]. In addition, these results confirm previous data on the distribution of STs in our country; as a matter of fact, the three STs identified are the most frequent in Italy. In particular according to the EWGLI records the ST1 is the most frequent, followed by ST23 and ST42. These STs strains are frequently isolated also in Europe [16, 17] and in other large geographic area such as Canada, China and Japan [7, 18, 19]. These findings support the hypothesis that some specific *L. pn. sg 1* clones have gained widespread dissemination probably due to a common ecological niche. The Apulia region can be consider a well-integrated part of European ecosystem where the most common sequence types of *L. pn. sg 1* appears to be not only ubiquitous and characterized by common epidemiological behaviors but also easily spreading.

Since Legionnaires' disease occurs both in sporadic and epidemic forms, a rapid molecular identification of *L. pn.* is strongly suggested to control epidemics and to identify the source of infection.

In conclusions, further researches are required to investigate the potential changing incidence of STs and the fitness of emerging strains or clonal groups in environmental strains too.

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# Urinary tract infection among intellectual disability individuals "Etiology and antibiotic resistance patterns" in rehabilitation centers of Mazandaran province, Northern Iran

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## Key words

Intellectual disability • Urinary tract infection • Rehabilitation center • Antimicrobial resistance • Iran

## summary

**Objective.** Urinary tract infections (UTIs) are amongst the most common infections and account for large proportion of antibacterial drug consumption. The aim of this study was to determine the rate and the etiologic agents of UTIs in inhabitants of rehabilitation centers of Mazandaran province in northern Iran and to evaluate the antimicrobial susceptibility patterns of the uropathogens isolated.

**Methods.** Clean catch midstream urine sample was collected from each of 314 participants (163 males, 151 females) residing in 12 rehabilitation centers of Ramsar, Nowshahr, Chalous, Amol, Sari and Behshahr. Urine specimens were cultured and bacterial isolates were identified by conventional methods. All urines fulfilling the criteria for the presence of significant bacteriuria ( $\geq 10^4$  cfu/ml urine) were defined as positive. Antibiotic susceptibility testing was performed by Kirby-Bauer disc diffusion method.

**Results.** The rate of urinary tract infection was 30.9% with the highest rate in pediatrics ( $p < 0.0001$ ). The prevalence of UTIs were shown to be higher in females than in males with the rate of 46.3% in young aged females (20-29 years), 60% in middle aged group (40-49 years) and 50% in elderly ( $> 50$  years). Bacteria most frequently isolated from urine specimens was *Escherichia coli* (39.2%) with the highest rate of infection in females age group  $< 10$  years ( $p < 0.001$ ). Among the antibiotics tested against the isolated organisms for susceptibility test, ceftriaxone and gentamicin maintain good activity against the majority of gram negative bacteria that cause UTIs recovered from individuals with intellectual disability. Vancomycin was effective against *Staphylococcus aureus*.

**Conclusions.** This survey shows that the prevalence of UTIs among inhabitants of institutions for mentally retarded persons in Mazandaran province of Iran is much higher than normal population.

## Introduction

Urinary tract infections (UTIs) are amongst the most common infections and account for large proportion of antibacterial drug consumption. Worldwide, about 150 million people are diagnosed with UTI each year, costing the global economy in excess of 6 billion US dollars [1, 2].

The etiology of UTI and the antibiotic resistance of uropathogens have been changing over the past years, both in community and nosocomial infection [3, 4].

The infections range from a single acute symptomatic infection, with a susceptible organism which may develop a spontaneous cure, to a more serious recurring infection such as chronic pyelonephritis which may be caused by resistant, and often difficult to treat, organisms.

Previous studies have shown that *Escherichia coli* is the predominant cause of UTIs both in and outside hospitals. Recent studies in North America and Western Europe demonstrated increasing resistance in UTI *E.coli* to ampicillin, trimethoprim and sulfonamides [5-8].

Since UTI is a very common infectious disease, all individuals are susceptible to urinary tract infections; however, the prevalence of infection differs with age, sex, and certain predisposing factors including mental abnormalities [9]. However, there is not only much information on etiology of UTIs among inhabitants of institutions for mentally retarded persons in Iran but also the susceptibility pattern of uropathogens is still unknown. We decided to analyze demographic characteristics and distribution of microorganisms causing UTIs in these individuals and to study their resistance pattern to antibiotics. This study is important for empiric treatment of individuals with mental retardation who have UTI and the data would also help authorities to formulate antibiotic prescription policies in rehabilitation centers.

## Materials and methods

This descriptive study was conducted between April and December 2011 on individuals with intellectual disability residing in 12 rehabilitation centers of Mazandaran prov-

ince, northern Iran. These centers had a total residential population of 660, of which, 32 patients that used antimicrobial agents in the previous 2 months were excluded from the study. However, since there was not published data on the rate of UTIs in patients with intellectual disability in Iran, the sample size was calculated as 314 participants on a prevalence of 50%,  $d = 0.05$  at a confidence level of 95%. Participants were 1-69 years old (mean =  $26.53 \pm 12.15$  years) and toilet themselves independently.

Freshly voided midstream specimens of urine ( $n = 314$ , 151 from females and 163 from males) were submitted to the clinical microbiology laboratory of Sari Medical School, Mazandaran University of Medical Sciences for processing. Data on age, gender, previous UTI and the use of antibiotics in the past two months were recorded for each individual.

Semi quantitative urine culture using a calibrated loop was used to inoculate blood agar and MacConkey plates [10]. The growth was quantified and bacteria were identified according to standard procedures [11]. A culture was defined as positive if  $\geq 10^4$  cfu/ml of probable urinary pathogens were found (significant bacteriuria). More than two microorganisms in one positive culture were considered as contamination.

Susceptibility test was performed using Kirby-Bauer disk diffusion method according to Clinical Laboratory Standards Institute (NCCLS) guidelines [12].

The antibiotic disks (Padtan Teb, Tehran, Iran) comprised: amoxicillin (10  $\mu\text{g}$ ), vancomycin (30  $\mu\text{g}$ ), tetracycline (30  $\mu\text{g}$ ), nitrofurantoin (300  $\mu\text{g}$ ), ceftriaxone (30  $\mu\text{g}$ ), ciprofloxacin (5  $\mu\text{g}$ ), gentamicin (10  $\mu\text{g}$ ) and trimethoprim-sulfamethoxazole (25  $\mu\text{g}$ ).

The research project was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran.

## Statistical analysis

Data were analyzed by the SPSS statistical package program. A descriptive univariable analysis was performed to evaluate the frequency of the variables. The associations between categorical variables were identified using the Chi-square and Fisher's statistical exact tests at a significant level of 5%.

## Results

Of 314 urine specimens processed, 97 (30.9%) showed significant bacteriuria. The rate of UTI was 19.2% for female subjects and 11.7% for male subjects. Distribution of Urinary tract infection in relation to gender and age of study population in rehabilitation centers of three geographical regions of Mazandaran province is shown in Table I.

The prevalence of UTI were shown to be highest in individuals residing in rehabilitation centers of western Mazandaran province (42.6%) with no statistically differences in male and female subjects ( $p > 0.05$ ). The lowest rate of infection were identified in residents of rehabili-

tation centers in center of Mazandaran province (17.5%,  $p < 0.0001$ ,  $X^2 = 21.93$ ,  $df = 2$ ), with predominance in females than in males (27.8% vs. 14.8%,  $p = 0.05$ ).

In this survey, the rate of UTI in female subjects age group  $< 10$  years was 100% ( $p < 0.0001$ ). This rate were shown 46.3% in young aged females (20-29 years), 60% in middle aged females (40-49 years) and 50% in elderly ( $> 50$  years). In male subjects, the highest rate of UTI were identified in age groups  $< 10$  years (75%,  $p < 0.001$ ) and in elderly (33.3%).

Of 97 significant isolates, gram-negative aerobic rods accounted for 85.5% while gram-positive cocci comprised the remaining 14.5% of the total pathogens. In the present study the most frequently isolated species from UTIs were *Escherichia coli* (*E. coli*) (39.2%) and *Enterobacter spp* (30.9%) followed by *Klebsiella pneumoniae* (9.3%), *Proteus spp* (6.2%), *Enterococcus fecalis* (8.2%) and *Staphylococcus aureus* (6.2%).

Table II presents the distribution of pathogens according to gender and age. *E. coli*, *Enterobacter spp* and *K. pneumoniae* were the major pathogens in two sexes. In  $< 10$  years aged female group, all isolates were *E. coli* with a constant reduction according to increase in age in favor of other uropathogens. In the  $> 50$  years old female groups, 33.3% of the positive cultures were due to *E. coli*.

In male subjects of  $< 10$  years, the lowest rate of UTIs was caused by *E. coli*, but an increasing in the isolation rate of this uropathogen according to increase in age with slight variation were noted. In elderly ( $> 50$  years), there was not significant differences in the rate of UTIs caused by *E. coli* in males and females ( $p = 0.1$ ).

*Enterobacter spp*, *K. pneumoniae* and *S. aureus* were more frequent isolates in males than in females with significant differences in pediatrics ( $p < 0.05$ ).

*E. fecalis* were responsible for UTIs more frequently in females than in males but the differences were not statistically significant ( $p = 0.2$ ). Resistance pattern to antibiotics is shown in Table III. The susceptibility testing profiles of *E.coli* showed low level of resistance against gentamicin (13.1%), tetracycline, ciprofloxacin, cotrimoxazole and nitrofurantoin (26.3% each). Sixty three percent of *E. coli* and 96.7% of *Enterobacter spp* isolates were fully susceptible to ceftriaxone. Of 38 *E. coli* isolated, 36.9% were shown moderate sensitivity to ceftriaxone. No resistance of *K. pneumoniae* and *Proteus spp* isolates against ceftriaxone and gentamicin were observed.

Resistance rate of *Enterobacter spp* to cotrimoxazole and ciprofloxacin was (86.6%) and (53.3%) respectively. Twenty of 30 *Enterobacter spp* isolated (66.6%) were susceptible to gentamicin and 33.3% have shown moderate susceptibility to the drug.

Three of 6 *S. aureus* strains isolated (50%) were susceptible to vancomycin and 100% of the isolates were susceptible to gentamicin. In *E. fecalis* the highest level of resistance to cotrimoxazole were identified (62.5%).

## Discussion

This study provides current information regarding the prevalence rate and the etiologic agents of UTIs in indi-

**Tab. I.** Distribution of UTIs by gender and age in individuals with intellectual disability residing in Rehabilitation centers of three geographical regions of Mazandaran province, northern Iran, 2011 (N = 314).

Rehabilitation centers	Male						Female					
	< 10 (N* = 12)	10-19 (N* = 30)	20-29 (N* = 45)	30-39 (N* = 24)	40-49 (N* = 37)	> 50 (N = 15)	< 10 N* = 1	10-19 N* = 27	20-29 N* = 54	30-39 N* = 47	40-49 N* = 20	> 50 N = 2
Central Province n (%)	5 (83.3)	2 (18.2)	3 (9.7)	0 (0)	2 (10.5)	1 (12.5)	1 (100)*	2 (14.3)	6 (35.3)	1 (25)	0 (0)	0 (0)
Western Province n (%)	4 (66.6)	3 (15.8)	3 (21.4)	6 (100)	4 (22.2)	4 (00)	0 (0)	3 (27.3)	17 (61)	13 (36.1)	11 (57.9)	1 (100)
Eastern Province n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	2 (22.2)	1 (14.3)	1 (100)	0 (0)
Total n (%)	9 (75)*	5 (16.6)	6 (13.3)	6 (25)	6 (16.2)	5 (33.3)	1 (100)*	6 (22.2)	25 (46.3)	15 (32)	12 (60)	1 (50)

\* (p &lt; 0.001).

**Tab. II.** Age and gender wise distribution and frequency of uropathogens isolated from individuals with mental retardation residing in rehabilitation centers of Mazandaran province, northern Iran, 2011.

Age groups	Uropathogens											
	E. coli		Enterobacter spp		K. pneumoniae		Proteus spp		E. fecalis		S. aureus	
	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)
< 10	22.2	100	44.4	0	11.1	0	11.1	0	0	0	22.2	0
10-19	40	33.3	20	33.3	20	16.6	0	0	20	0	0	16.6
20-29	66.6	36	33.3	32	0	8	0	12	0	12	0	0
30-39	33.3	40	33.3	40	0	6.6	16.6	0	0	6.6	16.6	6.6
40-49	50	40	16.6	30	16.6	10	0	0	0	10	16.6	10
> 50	40	33.3	20	0	20	0	0	33.3	20	33.3	0	0

viduals with mental retardation in northern Iran. Our findings enable the rate of UTI in individuals with intellectual disability to be compared with the rate of the infection in normal populations reported by other investigators.

Community acquired UTI is a predominant infectious disease especially in women. In this survey the proportion of UTI in female subjects were higher than in males (19.2% vs. 11.7%). Our results are consistent with recently published studies performed on different age groups in normal populations, which have been extensively reported that women have a higher prevalence of UTI than men, principally owing to anatomic, microflora and physical factors [9, 13-15].

Current survey showed that the rate of UTI among children (< 10 year age) with intellectual disability was higher than those of other age groups (100% in girls and 75% in boys). It should be noted that the total number of pediatrics residing in rehabilitation centers of Mazandaran province was lower than those of other age groups and most of them had UTI, so the rate of the infection represented higher in this group.

In our study the rate of UTI in inhabitants of rehabilitation centers of western Mazandaran province was higher than those residing in other institutions under study. These centers have certain limitations that are inherent to medical and laboratory base facilities. For example, some of rehabilitation centers of western Mazandaran

province are very far from academic institutions for medical cares which itself provides difficulties in the diagnosis and treatment of patients and influences on the number of such cases.

In our survey, the rate of infection caused by *E. coli* was 39.2% which is similar to those reported by other investigations in normal populations; 32% [16], and 40% [17]. With respect to the causes of UTIs in our series, the rate of UTI caused by *E. coli* was 100% in girls under 10 (p < 0.001), but the incidence decreased according to the increase in age with a little variation and persisted in elderly. Males presented an increasing in the isolation rates of *E. coli* up to 29 year age and with a slight variation its persistence were identified in elderly. These findings show that *E. coli* is the most common cause of UTIs in the residents of rehabilitation centers of northern Iran particularly in females with similar rate of incidence in normal populations as shown by many reports [7, 18-20].

*Enterobacter spp*, *K. pneumoniae* and *S. aureus* were moderately predominant in males. As known, UTI in men is often associated with diagnostic and/or therapeutic instrumentations in the genitourinary tract especially prostate; these procedures usually expose patients to UTI [21, 22]. In our survey therapeutic instruments were not used by any individuals residing in the centers under study. The higher rate of infection in males caused



Tab. III. Frequency and resistance pattern of uropathogens against antibiotics tested/

Microorganisms identified	No. of isolates & percent of occurrence			Percentage (%) of resistance against antibacterial agents					
		Co	Ci	Cf	G	T	Nf	V	AMP
<i>E.coli</i>	38 (39.2)	26.3	0	26.3	13.1	26.3	26.3	-	-
<i>Enterobacter spp</i>	30(30.9)	86.6	3.3	53.3	3.3	10	86.6	-	-
<i>K.pneumoniae</i>	9(9.3)	77.7	0	33.3	0	22.2	44.4	-	-
<i>Proteus pp</i>	6 (6.2)	100	0	100	0	33.3	66.6	-	-
<i>E.fecalis</i>	8(8.2)	62.5	-	12.5	12.5	12.5	-	12.5	12.5
<i>S.aureus</i>	6(6.2)	100	-	50	0	50	-	50	-

Co = cotrimoxazole; Ci = ceftriaxone; Cf = ciprofloxacin; G = gentamicin; T = tetracycline; Nf = nitrofurantoin; V = vancomycin; AMP = ampicillin.

by some of these bacteria may be due to the prostate problems that have not been identified and treated.

*Proteus spp* are rarely encountered in cases of community-acquired UTIs. In the present study, 6.2% of *Proteus spp* isolates were found to be present among all uropathogens studied, as shown by others [4, 13].

In individuals with mental retardation, the rate of UTI caused by *S. aureus* was 6.2% with predominance in males ( $p < 0.05$ ). There is an increased incidence of infection with *S. aureus* in association with urinary tract obstruction, neoplasm, and manipulation [23]. Prior to antimicrobial therapy, *S. aureus* was the leading cause of hematogenous infection of the kidney and perinephric abscesses.

The incidence of *E. fecalis* in our study was 8.2%, with the rates of 75% in females and 25% in males. Our data are consistent with Gupta et al. [24] and Rosa Daza et al. [25] findings, who have shown significantly higher proportion of UTI caused by *E. fecalis* in women.

Although there are not much published reports concerning UTIs in individuals with intellectual disabilities, the prevalence of the infection in our study (30.9%) is much higher than those of many other studies conducted in normal population in different parts of Iran including, in two pathobiology laboratories of Tehran 6.3% [26], in a 374-bedded educational hospital, Shiraz 1.82% [27] in 5136 samples from patients suspected of having UTI, northwest of Iran 13.2% [28] and in other countries, 5.9%, 18.89% and 27% [29-31], however the type and distribution of uropathogens isolated are similar to above mentioned reports. These differences in prevalence may result from host factors, environmental conditions, and practices such as health care and hygiene practices in different populations.

Antibiotic resistance is a major clinical problem in treating infections caused by most gram negative microorganisms. The resistance to the antimicrobials has increased over the years. Resistance rates vary from country to country. Overall, isolates from Latin American countries show the lowest susceptibility rates to all antimicrobial agents followed by Asian-Pacific isolates and European strains [4, 32-34].

In the present study most *E. coli* isolates from individuals with intellectual disability were susceptible to the drugs commonly used in general practice such as ceftriaxone, cotrimoxazole, ciprofloxacin, nitrofurantoin, gentamicin and tetracycline.

Regarding quinolones, nitrofurantoin and cotrimoxazole, even though we did not find statistical significances, there is a trend towards high resistance rates of other gram-negative bacteria rather than *E. coli* in our geographic area.

In the current survey, the rate of resistance against ciprofloxacin (53.3%, 100%, 33.3%), nitrofurantoin (86.6%, 66.6%, 44.4%) and cotrimoxazole (86.6%, 100%, 77.7%), among *Enterobacter spp*, *Proteus spp* and *K. pneumoniae* collected from residents of rehabilitation centers in northern Iran were high. *E. faecalis* showed no special resistance to the drugs habitually used in UTI except against cotrimoxazole. In the present survey, only 12.5% of *E. fecalis* isolates were resistant to the drug. The large use of antimicrobial agents in our geographic area during the past decade has contributed to the selection of a high number of resistant uropathogens.

In our study, while ceftriaxone and gentamicin presented good activity against the majority of isolates, vancomycin and gentamicin demonstrated excellent in vitro activity against *S. aureus* isolates recovered from UTI in individuals with mental retardation.

However, due to the narrow spectrum of antibiotics tested in this survey, no definitive conclusion can be drawn and the results cannot be compared with other reports in this respect. Data presented in this survey, indicates that the prevalence of UTIs among inhabitants of institutions for mentally retarded persons in north and central regions of Mazandaran province are lower than in western areas. Our findings indicate that sponsors and staff of these institutions are fully trained for taking care of individuals with mental retardation and have medical knowledge regarding control and prevention of UTIs in these individuals. Antibiotics commonly used in UTIs are still effective, but species distribution and their susceptibility to antibiotics are changing in general all around the world. It requires regular monitoring in order to make reliable information available for optimal empirical therapy of UTIs among inhabitants of rehabilitation centers.

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# Anti-rods and rings autoantibodies can occur in the hepatitis c-naïve population

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## Key words

Autoimmunity • Autoantibodies • Hepatitis C

## Summary

**Introduction.** *The anti-Rods and Rings autoantibody recently described in clinical populations is thought to occur in the setting of hepatitis C treatment, specifically in the context of cytidine triphosphate (CTP) and guanosine triphosphate (GTP) synthetic pathway inhibitors, and is important in its potential impact on response to therapy. This study asks the question: what is the epidemiology of anti-RR autoantibody in the general, non-clinical population?*

**Materials and methods.** *This is a cross-sectional study using the National Health and Nutrition Examination Survey (NHANES). Immunofluorescence assay for anti-Rods and Rings autoantibody were performed by NHANES labs and the results made publically available. Sample weights were used to calculate the prevalence and distribution of the autoantibody across demographics. A medication profile of the autoantibody positive population was also constructed.*

**Results.** *The study sample consisted of 4738 persons over the age of 12 years. Anti-Rods and Rings autoantibodies were found in 39 persons representing 1.3 million persons in the United States population. 38 of 39 persons with anti-Rods and Rings autoantibody had no prior history of hepatitis C virus infection. A majority of these persons were found to have poly-pharmacy.*

**Discussion.** *This is the first study to show that anti-RR can occur in the general population without evidence of hepatitis C virus infection, and that the majority of persons with anti-RR in the population have no evidence of prior hepatitis C infection. This indicates that there may be another undetermined etiology for anti-rods and rings autoantibodies besides the currently accepted exposure etiology of hepatitis C virus infection and treatment found in clinical studies.*

## Introduction

Studies have recently described a new cytoplasmic organellar complex that is morphologically toroidal, also occurring as rods and rings [1, 2]. These structures have been shown to be evolutionarily conserved and have been observed in a number of organisms including *Drosophila* [3], rats [1] and yeast [4] in addition to their detection in humans [2, 5-7]. Clinical studies have found that patients positive for anti-rods and rings autoantibodies (anti-RR) tend to be HCV positive [2], have been treated by combination interferon (IFN) and/or ribavirin therapy [2, 8, 9], and are poorer responders to therapy [9]. It is thought that occurrence of anti-RR in persons with HCV may be secondary to its treatment using IMPDH2 inhibitors such as ribavirin leading to intracellular aggregation of IMPDH2 thereby altering its immunogenicity [8]. Past clinical studies have shown that anti-RR can be found in up to 35% of HCV infected persons [8], most often in those being treated with IFN/ribavirin combination therapy and not typically in uninfected persons or prior to antiviral therapy [9]. Studies thus far have been conducted primarily on clinical populations. We set out to answer the question: what is the epidemiology of anti-RR in the general population? We intend to investigate the prevalence of anti-RR in the US non-clinical population, investigate the distribution of this autoantibody by

population demographics and examine what proportion has evidence of prior HCV infection. This investigation is relevant to medical practice because amongst the HCV infected persons where it has been studied anti-RR status is thought to impact response to therapy [9].

## Materials and methods

### STUDY DESIGN

This study is a cross-sectional analysis of data from multiple years (1999-2004) of the National Health and Nutrition Examination Survey (NHANES) administration.

### SURVEY DESIGN AND DATA COLLECTION

The NHANES has a non-random, complex, multi-stage, probability sampling design [10]. The sample is representative of the non-institutionalized US population with over-sampling of persons 60 and older, African Americans, and Hispanics [10, 11]. Interview and examination data is collected based on Institutional Review Board approval from the National Center for Health Statistics Research Ethics Review Board.

Given that anti-RR antibodies are rare phenomenon, 3 cycles of the continuous NHANES were combined to

produce estimates with greater statistical reliability. In total, 31,126 persons participated in the NHANES 1999-2004 [12]. Of these, 29402 persons (94.5%) completed both the interview and the examination portions, from which 7106 persons (23% of total sample) were randomly selected to be included in the subsample whose sera was tested for autoantibodies. From this subsample 4738 persons (15% of total sample) had complete data for anti-RR and HCV antibody, constituting the study sample [12].

**LABORATORY TESTING**

Data on anti-RR autoantibodies were obtained from the 1999-2004 NHANES files. The details of the procedures involved in testing of IgG autoantibodies to human cellular antigens can be found in the respective documentation on the NHANES website as well as in the study on US prevalence of Antinuclear Antibodies in the US by Satoh et al. [13]. Immunofluorescence assays were used by NHANES associated labs to detect autoantibodies using anti-human IgG [13], with staining intensities for anti-RR of 1 or more defined as positive and codified in a separate variable [12].

HCV antibody testing was conducted on all examinees 6 years and older. Antibodies directed against hepatitis C virus (anti-HCV) were measured from serum or plasma using direct solid -phase enzyme immunoassay with the anti-HCV screening ELISA. Positive specimens were reanalyzed with the same procedure, with those that were repeatedly positive tested using the Chiron RIBA Processor System (Chiron Corporation, Inc.), an in vitro qualitative enzyme immunoassay for the detection of anti-HCV [14]. Samples where the RIBA result was positive were reported as confirmed positive for antibody to HCV, while those with a negative RIBA result

were reported as negative, and indeterminate results are reported as indeterminate [14].

C-Reactive Protein (CRP) in serum was quantified using latex-enhanced nephelometry, in which a dilute solution of test sample is mixed with latex particles coated with mouse monoclonal anti-CRP antibodies, allowing CRP present in the test sample to form an antigen-antibody complex with the latex particles [15].

Interviews for demographic and health information were conducted by the NHANES in respondents' homes using the computer-assisted personal interviewing (CAPI) method. Health examinations were performed in mobile examination centers. All lab procedures were performed by NHANES associated labs with the resulting variables available in datasets categorized by iteration.

**STATISTICAL ANALYSIS**

Statistical analysis was conducted taking into account the non-random, multi-stage probability sampling methodology of the NHANES dataset. Sampling errors were estimated using the Taylor series (linearization) method with survey design variables for strata and primary sampling units included in statistical survey procedures using the respective variables provided in the data files. Appropriate subsample weights associated with the antinuclear antibodies (ANA) data were used to generate national weighted estimates and to account for the complex survey design (including oversampling), survey non-response, post-stratification, stage of selection and additional non-response for the subsample. The prevalence of anti-RR in the US population was calculated stratified by demographic characteristics. (Tab. I) Demographic characteristics of subjects with and without Anti-RR antibodies were analyzed and Chi-Square tests were performed for comparison with a  $p < 0.05$  design-

Tab. I. Demographic characteristics by anti-Rods and Rings autoantibody (anti-RR) status.

DEMOGRAPHIC CHARACTERISTICS		(-) Anti-RR <sup>†</sup>		(+) Anti-RR <sup>†</sup>		p-value
		%	SE <sup>*</sup>	%	SE <sup>*</sup>	
<b>TOTAL</b>		<b>4699</b>		<b>39</b>		
Age,y (mean)		42.9	0.4	48.1	2.6	0.05
<b>Gender</b>						<b>0.5</b>
	Male	48.2	0.9	54.6	10.1	
	Female	51.8%	0.9	45.4%	10.1	
<b>Ethnicity</b>						<b>0.2</b>
	Non-Hispanic White	70.5	1.8	52.6	11.5	
	Hispanic	13.2	1.5	20.1	8.1	
	Non-Hispanic Black	10.7	1.1	20.7	6.0	
	Other	5.6	0.6	6.6	5.2	
<b>Education</b>						<b>0.2</b>
	Less than highschool	26.3	0.9	35.9	9.2	
	High school diploma	23.4	1.2	10.9	5.4	
	More than high school	50.2	1.2	53.2	9.7	
<b>Family Income-to-Poverty Ratio</b>						<b>0.9</b>
	At or Above Poverty Level	85.6	1.0	86.8	6.8	
	Below Poverty	14.4	1.0	13.2	6.8	

<sup>†</sup> anti-Rods and Rings autoantibodies; <sup>\*</sup> weighted Standard Error.

nating statistical significance. (Tab. II) The distribution of anti-RR over the known etiologies of HCV infection and treatment were calculated using survey questionnaire, medication use data and serum antibodies for HCV status. (Tab. III) Additionally, the medication usage profile of the anti-RR positive, HCV naïve population was investigated. (Tab. IV) Appropriate sample weights, stratification, and clustering design variables

were incorporated into all SAS survey procedures to ensure correct estimation of sampling error. Special Dioxin subsample weights are required to analyze the NHANES ANA data as it was generated using a randomly selected 1/3 subsample of each 2-year NHANES cycle (the Dioxin subsample). The 6-year subsample, interview and examination weights were calculated for the combined 1999–2004 data by following the NHANES

Tab. II. Estimated US prevalence of anti-rods and rings autoantibodies (anti-RR\*) by demographic characteristics.

DEMOGRAPHIC CHARACTERISTICS		n	Population positive for Anti-RR* (n)	% Population positive for Anti-RR* (95%CI <sup>†</sup> )
<b>TOTAL</b>		<b>4738</b>	<b>39</b>	<b>0.7 (0.4,1.1)</b>
<b>Age, years</b>				
	12-19	1188	7	0.6 (0, 1.2)
	20-29	684	4	0.5 (0,1.1)
	30-39	639	5	0.3 (0,0.6)
	40-49	578	2	0.5 (0,1.3)
	50-59	474	11	1.8 (0.5,3.0)
	60-69	523	3	0.7 (0,1.4)
	> 70	652	7	1.1 (0.2,1.9)
<b>Gender</b>				
	Male	2276	22	0.8 (0.4,1.3)
	Females	2462	17	0.7 (0.2,1.1)
<b>Ethnicity</b>				
	Non-Hispanic White	2111	13	0.6 (0.2,1.0)
	Hispanic	1446	13	1.1 (0.3,2.0)
	Non-Hispanic Black	992	11	1.4 (0.6,2.3)
	Other	189	2	0.9 (0.2,1.1)
<b>Education</b>				
	More than high school	1658	17	0.8 (0.3,1.3)
	High school diploma (GED)	896	5	0.3 (0,0.7)
	Less than high school	2178	17	1.0 (0.4,1.6)
<b>Family Income-to-Poverty Ratio</b>				
	At or Above Poverty Level	3357	30	0.7 (0.4,1.0)
	Below Poverty	980	4	0.6 (0,1.4)

\*anti-Rods and Rings autoantibodies; † Weighted Confidence Interval.

Tab. III. Estimated US prevalence of anti-Rods and Ring autoantibodies by selected anti-HCV\* antibodies status, CRP<sup>†</sup> levels and anti-viral therapies.

		n	(+) Anti-RR <sup>‡</sup> (n)	% (+) Anti-RR <sup>‡</sup> (95%CI <sup>§</sup> )
<b>anti-HCV*</b>				
	Absent	4658	38	0.8 (0.4,1.1)
	Present	80	1	0.1 (0,0.3)
<b>CRP<sup>†</sup> Categories</b>				
	< 1	4286	34	0.8 (0.4,1.1)
	1 to 3	387	4	0.4 (0,1.0)
	> 3	65	1	0.8 (0,2.2)
<b>Interferon + Ribavirin combination use</b>				
	Absent	4752	39	0.7 (0.4,1.1)
	Present	2	0	-
<b>Interferon use only</b>				
	Absent	4749	38	0.7 (0.4,1.1)
	Present	5	1	-
<b>Ribavirin only</b>				
	Absent	4753	39	0.7 (0.4,1.1)
	Present	1	0	-

\*Hepatitis C Virus; † C-Reactive Protein; ‡ anti-Rods and Rings autoantibodies; § Weighted Confidence Interval.

**Tab. IV.** Medication Profile of Hepatitis C virus-naïve, anti-Rods and Rings autoantibody (+) Population.

	n	%
<b>MEDICATION CLASSES</b>		
Antihypertensives	8	38.1
Anti-GERD*	5	23.8
Albuterol	3	14.3
Synthetic hormones	3	14.3
Anti-clotting medications	2	9.5
Other	11	52.4
<b>POLY-PHARMACY</b>		
4+	4	19.0
3	4	19.0
2	4	19.0
1	9	42.9

\*GERD: Gastroesophageal Reflux Disease.

analytic and reporting guidelines. The Dioxin weights (WTSP04YR for 1999-2002 and WTSC2YR for 2003-2004) were used for the subsample. One-third of the respective 2-year weights for 2003-2004 were used and merged with two-thirds of the 4-year 1999-2002 respective weights [16]. All analysis was performed using SAS 9.2 (SAS Institute, Cary, NC).

## Results

In this sample of 4738 persons over the age of 12 years, 39 persons were found to be positive for anti-RR (Tab. I), the outcome of interest, representing a prevalence of 1.3 million (95% CI: 0.7-1.9 million) persons in the US population. The mean age of the population was comparable across anti-RR status (42 years old *vs.* 48 years old for negative and positive respectively). The two groups had approximately equal proportions of males and females, were more likely to be non-Hispanic White, with more than high school level of education, and above the poverty level (Tab. II).

Of all person who were anti-RR positive ( $n = 39$ ), only one was found to have had prior HCV infection. Conversely, anti-HCV was found in 80 persons who were almost all anti-RR negative (79 negative *vs.* 1 positive). The use of HCV therapy was examined to determine the influence of CTP and GTP synthesis inhibitors. However, of participants currently using Ribavirin and/or IFN, only one also tested positive for anti-RR. Inflammation, marked by CRP, was not associated with anti-RR status.

Because prior studies have shown an association with medication usage (for HCV therapy) and anti-RR status, medication use amongst HCV-naïve but anti-RR positive persons was calculated. Medication use was reported by 21 of the 39 persons positive for anti-RR with one person reporting IFN usage (Tab. IV). Over half of these (11/21) had polypharmacy and over a third (8) were antihypertensives. Usage of medications with CTP or GTP synthetic pathway inhibition activity was not prevalent in this population.

## Discussion

In this analysis of the US non-institutionalized population, the overall prevalence of anti-RR was found to be 0.74%, signifying 1.3 million persons. Persons with and without anti-RR were found to be similar across demographic characteristics.

This study found that the majority of anti-RR prevalence was found to occur without prior exposure to HCV and its therapy. In contrast, prior studies of clinical populations have suggested that a majority of anti-RR occurs in the context of HCV infection and treatment [1, 2, 8, 9]. The fact that more persons with a past history of HCV were not found to have anti-RR may be partly explained by the transience of some forms of anti-RR as reported in prior literature [17]. The fact that more persons with anti-RR and HCV infection were not found in the general population would not be surprising if anti-RR typically cleared in the post-therapy period. From this context, it is likely that the ever-positive status of anti-RR could significantly be higher in the population of persons having been infected by HCV and having gone through its treatment. This association would subsequently be hard to detect in the general, non-clinical population as the baseline levels of the autoantibody would exist with no trace of induced antibodies in the ever-positive population. Although this hypothesis was tested by examining the population of persons currently using IFN, or ribavirin or a combination of both, the analysis was limited by the small proportion of persons reporting usage of these medications.

In regards to the existence of anti-RR in persons without evidence of prior HCV infection, this finding is corroborated by implicit findings of an earlier study that showed that anti-RR can in fact also occur in persons independent of an antecedent HCV infection. In a 2010 study by Carcamo et al it was demonstrated that 15/23 persons with anti-RR had prior infection with HCV, indicating that 8/23 persons had anti-RR without prior HCV infection [17].

The question that arises from our findings is whether there is a difference between the type of anti-RR found in persons infected with HCV with subsequent treatment versus HCV-naïve persons. A difference in the etiology or physiology is suggested by the high prevalence of anti-RR without evidence of prior HCV infection. If HCV infection played a more substantial role then its history would be more prominent amongst anti-RR positive persons, even if the antibodies are transient. However if the transience of the antibodies is impacted by their cause (HCV treatment versus other than HCV treatment) then it better explains the findings of a large number of people having those antibodies but no history of HCV. The implications for the finding of anti-RR in HCV-naïve persons is that either these antibodies are elicited through the same pathways associated with HCV treatment or by another pathway that has not yet been characterized. If the former is considered, then anti-RR may be induced in HCV-naïve persons by diseases, medications or environmental factors that inhibit the CTP and GTP synthesis pathways.

This study has several limitations including the small population prevalence of anti-RR, which prevented a more thorough statistical analysis for associations. Furthermore, the primary risk factor for anti-RR has been found to be ribavirin and IFN combination therapy, however the prevalence of this was also very low. Additionally, given the cross-sectional study design it was not possible to determine the transiency or permanence of anti-RR, which can impact prevalence and associations.

While the limitations and/or differing mechanisms prevent verification of findings derived from prior studies of clinical populations, the strength of this study is that its large nationally representative sample indicates that where findings are positive these are worthy of further investigation. One such finding of importance is that anti-RR positivity can in fact occur in the general population outside of the context of hepatitis C infection and its treatment. This indicates that in addition to the identified pathways in HCV positive persons, there may possibly be other factors or pathways in HCV-naïve persons, possibly involving polypharmacy or chronic conditions, which may be associated with cytoplasmic rods and rings induction and/or anti-RR formation. Furthermore, this study presents a baseline population estimate of anti-RR prevalence so that future studies can monitor trends. Since anti-RR and their target cytoplasmic rods and rings structures have only recently been identified, the cause of these newly discovered autoantibodies in the general population, their role in health and disease, the clinical consequences of their presence, and their

natural history are all questions that remain and require further investigation.

## Conclusions

In conclusion, this study found that there are approximately 1.3 million persons in the US who are positive for anti-RR, the vast majority of whom have no circulating antibodies to the hepatitis C virus and therefore no evidence of a prior immune response to its infection and no active treatment individually or in combination with ribavirin and IFN. This study is significant in its finding that the anti-RR autoantibody normally associated with HCV infection and treatment can also be found in the general HCV-naïve population. This study has implications on the possible temporal dependency of anti-RR and additional etiologies for its onset, thereby providing directions for future investigation: long-term follow-up studies can help establish the relationship of time with detectability of anti-RR; further investigation of non-HCV related anti-RR may help identify relationships with clinical presentations, particularly with chronic disease given the extent of prescription usage found in this study; and comparisons of non-HCV and HCV related anti-RR can help determine if there is a difference in anti-RR transience based on etiology and, if so, factors promoting clearance versus persistence may reveal insights into autoimmunity and therapy.

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# Suspension of mandatory vaccination and public health preserving: Rovigo Local Health Unit experience after appliance of Veneto regional law 7/2007

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## Key words

Mandatory and recommended vaccinations • Regional Law 7/2007 • Immunization coverage rates

## Summary

*The burden of infectious diseases preventable by vaccination decreased considerably over last decades in all countries provided with effective immunization schedules. Implementation of these programs with new vaccines has started discussion on duality between mandatory and recommended vaccinations. Regional autonomy has allowed the Veneto Region, with introduction of Law 7/2007, to experience suspension of all mandatory childhood vaccinations, replaced by an active and free offer of all vaccines recognized as safe and effective. Coverage's trends and acceptance of invitation are carefully monitored to avoid loss of compliance and reduction of immunized children. The evaluation, performed on population of Rovigo ULSS18 for 2002-2008 birth cohorts (2008 is the first concerned by the change), revealed no fall for previously mandatory vaccinations, but rather a slight increase. Percentage of non-vaccinated children was negligible.*

*The leading cause of non-vaccination to polio was inability to deliver the letter of invitation due to wrong address. An informed dissent was expressed only by a minority (0.9% in 2008 birth cohort).*

*Compliance to immunization offer was elevated both for previously compulsory and recommended vaccinations. Experience of Rovigo ULSS 18 showed that, in a context of already high levels of coverage for recommended vaccinations with optimal organization of immunization services, coverage rates for ex-mandatory vaccines remain unchanged. Further research and reports are required to carefully assess the effect on coverage rates in next birth cohorts, but available data are encouraging. Similar legislative measures can be successfully adopted by other Regions with starting conditions comparable to Veneto Region.*

## Introduction

Vaccinations are an effective prevention tool for maintaining the health of the individual and society as a whole and have significantly increased life expectancy and quality [1, 2]. Smallpox was officially declared eradicated by the World Health Organization (WHO) in 1980, all industrialized countries are considered "polio-free", while other important infectious diseases such as diphtheria, tetanus and hepatitis B reached a significant reduction [3-5], with important benefits for childhood, by the planning of vaccination campaigns and development of national pediatric immunization schedules in many European countries [6, 7].

Strategies adopted by European Union countries to achieve and maintain high immunization rates in target population include compulsory and recommended vaccinations, free of charge and co-payment offer. Some countries have preferred mandatory vaccinations such as France, Greece, Portugal and Italy (for some pediatric vaccines); others, such as the United Kingdom, voluntary decision supported by appropriate service offer, incentive for caregivers and health education. Others, like USA, Canada and Germany, opted for a middle way (no

sanctions for non-vaccination, but need for a certificate of admission to school) [8-10].

According to latest edition of national immunization schedule, Italian children are mandatory vaccinated against polio, diphtheria, tetanus and hepatitis B, while vaccinations against pertussis, measles, mumps, rubella, pneumococcus, meningococcus and invasive forms of *H. influenzae* type B are recommended [11]. This difference is merely theoretical since no coercion is actually performed for parents who express their dissent to compulsory vaccinations.

Accomplishment of mandatory vaccinations and successful extensive immunization programs permitted prevention of many infectious diseases which resulted in lower concern about them while, nowadays, worsening attention to side effects and availability of new vaccines has progressively increased burden of commitment within vaccination policy. Current scenario is also complicated by strongly varied regional framework in immunization schedules (determined by modification of Title V of Constitution), by inadequate information on low risk in terms of safety and significant benefits concerning protection that facilitate activity of antivaccinal groups.

All Italian National Vaccine Plans (NVP), from 2005 to present, notice the opportunity to begin a cultural and social awareness growth to overcome difference between compulsory and recommended vaccinations, inviting to same active offer for both vaccine groups, in favor of a modern approach, based on health education, health promotion and patient self-determination. Regions which possess following characteristics are encouraged to move towards abolition of mandatory vaccinations: an effective information system with well organized vaccines register; adequate immunization coverage; a sensitive and specific surveillance system of communicable diseases, are able to mix corporate/regional data flows; a good system of monitoring vaccine adverse events, are able to ensure appropriate follow up of cases.

Piedmont, for example, introduced in 2006 a method of simplification of immunization offer, defining priority vaccines (proposed free and in active manner) and all other vaccines (available in health care organizations at cost) obtaining very satisfactory results in terms of agreement [12]. Tuscany, instead, eliminated distinction between mandatory and recommended vaccinations in 2007 and 2010 through Tuscan Vaccine Schedules [13, 14]. Only recently [15] Autonomous Province of Trento started a step-by-step overcoming of compulsory vaccination in children, depending on achievement of provincial immunization coverage percentage not less than that expected by the NVP and in absence of conflicting epidemiological evaluations.

With Regional Law 7/2007 "Suspension of mandatory vaccination for children and adolescents" [16], Veneto Region has suspended obligation of compulsory immunizations for all infants born from 1 January 2008, confirming that they still are included in essential level of assistance and therefore free and actively offered by the Local Health Units (ULSS) and part of immunization schedule, periodically reviewed and approved by the Regional Council in accordance with NVP guidelines. A monitoring plan of vaccination system, shared with Ministry of Health and Superior Institute of Health, must ensure vaccination coverage achieves at least 95% of newborns, otherwise obligation suspension is stopped. President of Regional Council may also come back to previous system, if significant epidemiological events occur or if the content of the document drafted by the Technical Scientific Committee, expressly created, signals an alarm situation with regard to immunization coverage rates.

This paper aims to analyze whether innovations introduced by Veneto Regional Law 7/2007 have modified immunization coverage rates and parents participation in vaccination acceptance. Levels of vaccination coverage achieved in Local Health Unit of Rovigo (ULSS18) at 24 months in children born in 2002-2008 regarding immunizations for which obligation is suspended (including an estimate of non-vaccination against polio percentage and reasons for non-vaccination) and immunization rates for some recommended vaccinations (pertussis, *H. influenzae* B, measles, mumps and rubella) are considered.

For birth cohorts 2006-2011, we assessed percentage of children who have received, within the first year of life, full or partial cycle of vaccination against diphtheria, tetanus, pertussis, hepatitis B to detect possible differences between before and after the appliance of Regional Law 7/2007. Similarly we considered non-compulsory vaccinations against pneumococcus (partial and complete cycle), meningococcal C, measles-mumps-rubella (MMR) and chickenpox (one dose) to examine whether high levels of adhesion to recommended vaccinations were confirmed even after suspension of compulsory vaccination.

## Materials and methods

Records were obtained from two regional forms adopted for monitoring vaccination activities: Model 19 for coverage rates and Enclosure C for immunization acceptance. In both cases adjusted rates were calculated by dividing number of administered doses by number of children born in investigated cohort excluding unreachable (e.g. domiciled abroad and untraceable).

### IMMUNIZATION COVERAGE RATES

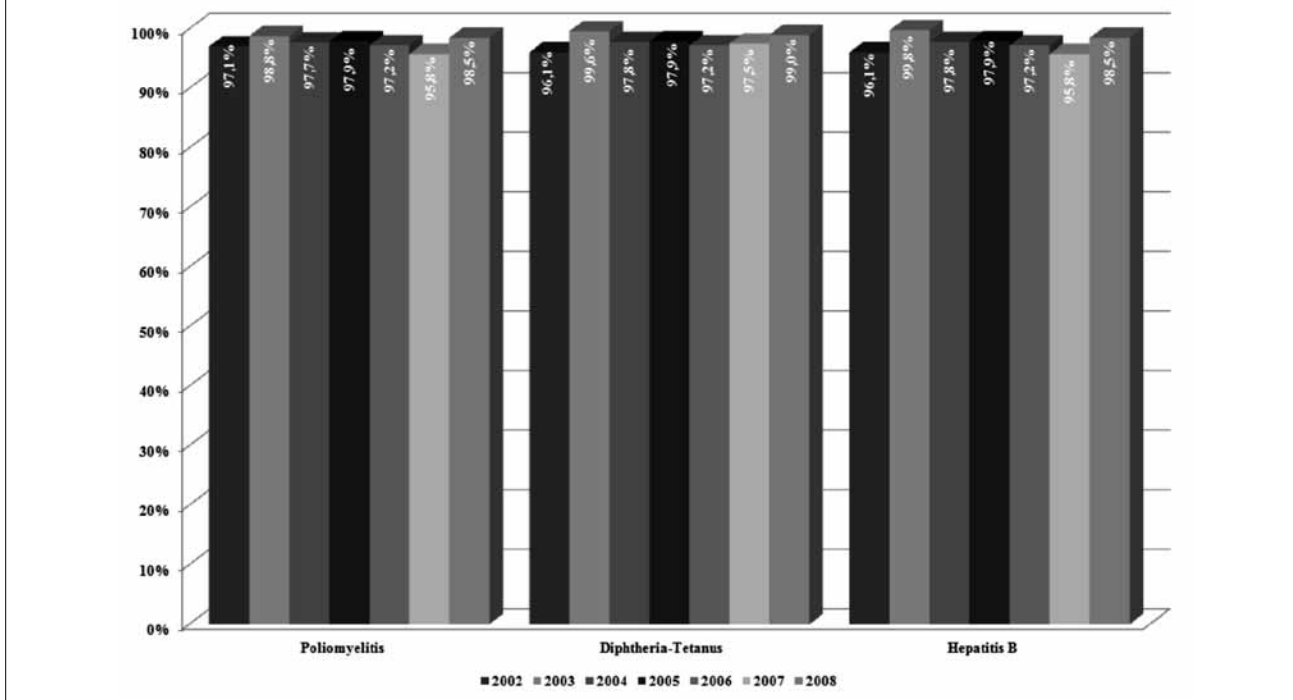
Data on immunization coverage were collected from annual survey form (so called Model 19) that each ULSS annually transmit to Veneto Region in order to assess coverage rates. Years from 2004 to 2010 were considered, therefore, vaccination coverage refers to birth cohorts 2002-2008 (2008 birth cohort is the first affected by the suspension of immunization compulsoriness). According to regional directives, we examined immunization coverage at 24 months as the number of completed vaccinations in children born two years before the year of reference. Coverage rates at 24 months were assessed as well as for previously mandatory vaccines (polio, diphtheria, tetanus and hepatitis B) as for those against pertussis, *H. influenzae* B (HiB), measles, rubella and mumps.

In addition, qualitative analysis of reasons for polio non-vaccination was performed.

### COMPLIANCE TO VACCINATION PROPOSAL AFTER SUSPENSION OF OBLIGATION

Trends in immunization offer acceptance were calculated from regional form, called Enclosure C, that each ULSS send to Department Prevention Services - Promotion and Development of Hygiene and Public Health of Veneto Region twice a year (March 31 and September 30) in order to strictly monitor vaccination compliance. Number of doses administered to newborns divided in cohorts, according to three previous semesters are recorded, e.g. the detection of 30 September 2011 considered separately children born in the first half of 2010, those born in the second half of 2010 and those born in the first half of 2011 in order to assess vaccines received within 6, 12 and 18 months from birth respectively. Presented data relate to three doses of hexavalent and anti-pneumococcal vaccines

Fig. 1. Rovigo ULSS18 coverage rate at 24 months for formerly mandatory vaccinations (birth cohorts 2002-2008).



and first dose of measles, chickenpox, rubella, mumps and meningococcal C vaccines in the period September 2007- September 2011.

## Results

Coverage percentages at 24 months for the vaccines for which suspension of compulsory immunization was introduced are shown in Figure 1. For each vaccination and for each birth cohort considered, 95% coverage, set by Region as goal, was always exceeded. For birth cohort 2008 percentage of vaccinated children, that under mandatory tended to decrease, showed an increase compared to previous birth cohort, reaching 98.5% for polio and hepatitis B and 99% for diphtheria-tetanus.

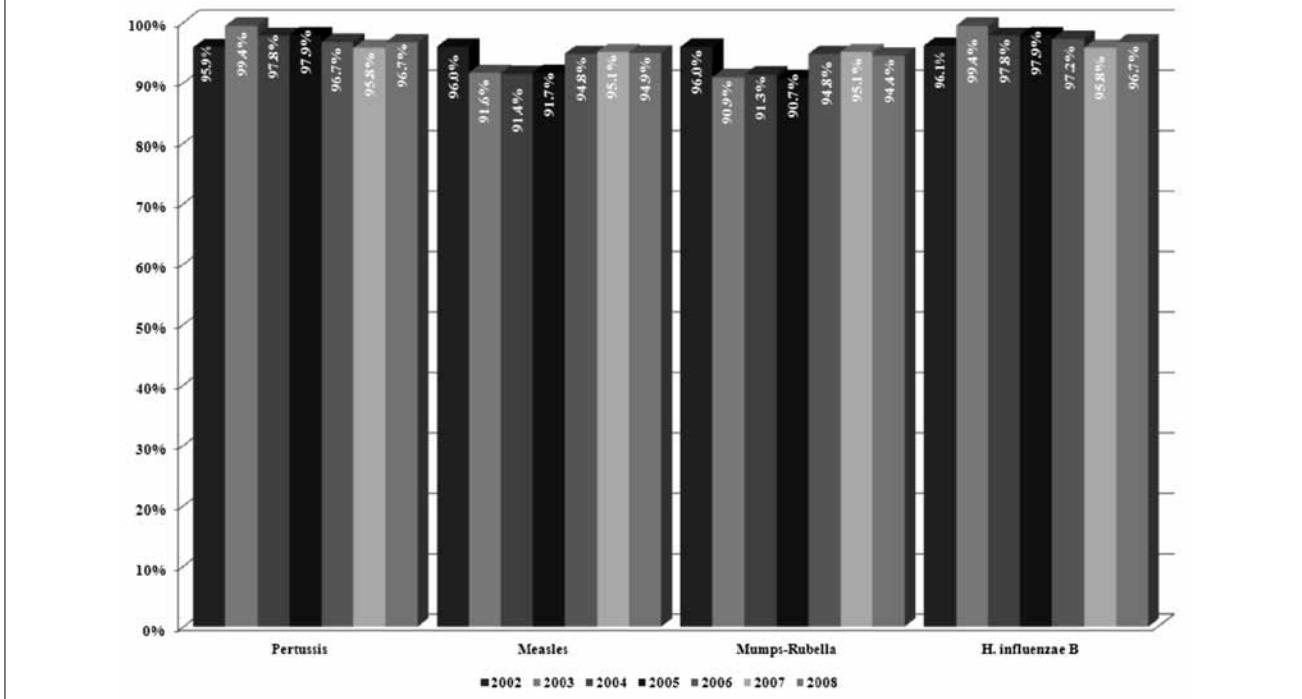
Figure 2 refers to formerly recommended vaccinations. The percentage of children vaccinated against pertussis and HiB at 24 months after birth was always fully satisfactory and, in the first cohort affected by the suspension of obligation, amounted to 96.7%. Measles, mumps and rubella vaccinations, that in cohort 2002 recorded a coverage of 96%, has shown, over the years, a marked reduction, however, in recent years percentage of vaccinated children has increased to 94.9% for measles and 94.5% for mumps and rubella.

The motivations of non-vaccination against polio at 24 months after birth are indicated in Figure 3. The leading cause was the inability to contact parents and deliver invitation to vaccination because they moved abroad, do not have a fixed address or are untraceable. Exemptions for health reasons have been sporadic and did not occurred after 2005.

Since 2007, standard definitions to define several types of vaccination postponement have been broadened considering also vaccination delay. Proportion of children actually defaulting vaccination (having expressed an informed dissent) was a minority, but the percentage showed an increasing trend from 0.2% in 2002 cohort to 0.9% in 2008 cohort.

Suspension of compulsory vaccination requires a closely monitoring of the compliance to immunization offer. Data collected every six months, before and after suspension of compulsory vaccination, are reported in Table I. The monitoring do not have the purpose of determine vaccine coverage, that can be estimated on consolidated data at 24 months of life, but to evaluate performance of immunization activities on cohorts of newborns to make a comparison over time and between ULSS (benchmarking), therefore it should not concern the detection of percentages slightly lower than 95% even for previously mandatory vaccinations. Proportion of children receiving hexavalent vaccine has always been elevated and a steady increase, more pronounced for the third dose, has been recorded. In all measurements, the percentage of vaccinated children has reached levels ranging from acceptable (90-94%) and desirable ( $\geq 95\%$ ). Vaccination against pneumococcal presented a comparable situation, with a more marked rise for third dose passing from 33% in September 2007 to 64% in September 2011. Percentage of children vaccinated against meningococcal (offered from the thirteenth month) was stable around 90%. Measles-mumps-rubella and chickenpox vaccinations starting from very lower rates of acceptance (respectively 72.3 and 67.3%) showed an increase, reaching levels fairly above 80%, always remaining within a not satisfactory range.

Fig. 2. Rovigo ULSS18 coverage rate at 24 months for formerly recommended vaccinations (birth cohorts 2002-2008).



## Discussion and conclusions

Regional autonomy has allowed, in healthcare sector, the undertaking of an important initiative of Public Health such as that started by Veneto Region with the promulgation of Regional Law 7/2007 that, overcoming the dichotomy between mandatory and recommended vaccinations, meets the growing demand of citizens for self-determination in choices regarding their health by introducing a legislative action with a European outlook. The debate on recommended or mandatory vaccinations has also collected conflicting opinions because it raises several ethical issues. The possibility for Regions to independently determine vaccination schedule and introduce new vaccines and methods of promotion has created a national framework strongly non homogeneous which could have a negative impact on immunization programs and, apparently, does not ensure equal access

to immunization. Furthermore, at first sight, the comparison between countries that only recommend certain vaccinations and countries that force them does not seem to show remarkable differences [17, 18].

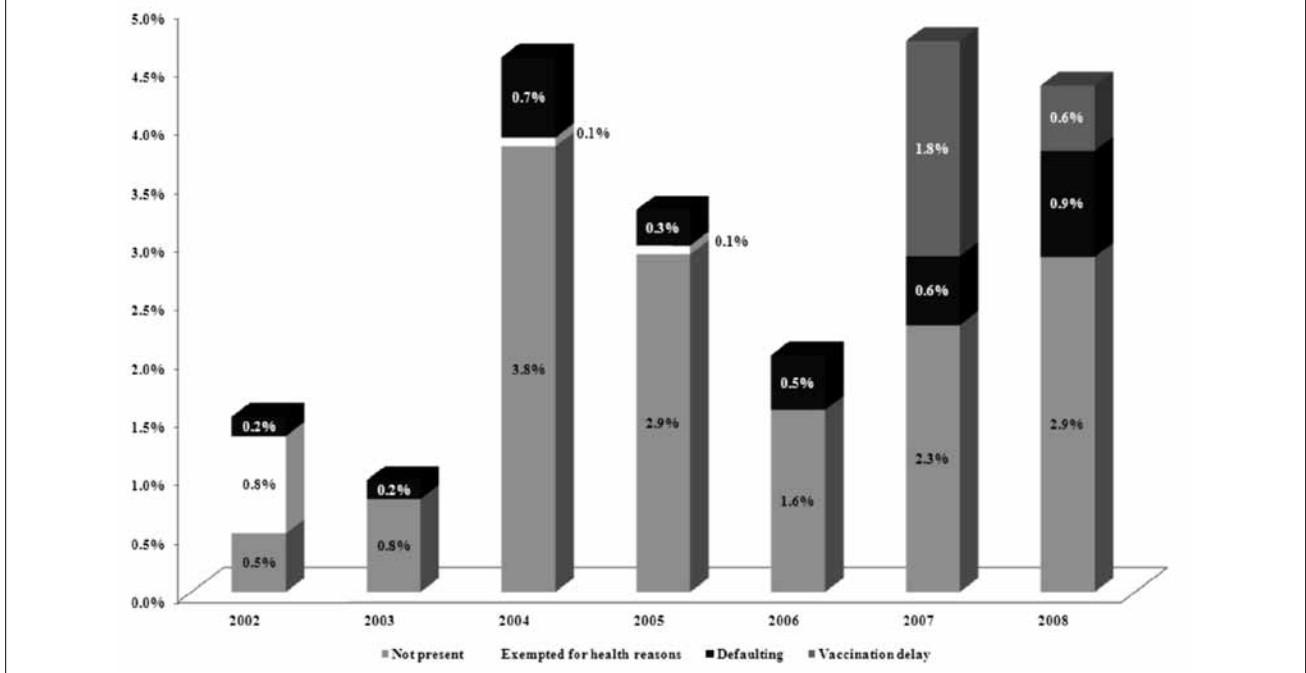
The experience of Rovigo ULSS18 showed that, in a context of already high levels of coverage for recommended vaccinations, rates for ex-mandatory immunizations remain unchanged. Results obtained in the 2008 birth cohort, the first involved in the suspension of the obligation, showed that no loss of coverage occurred for previously mandatory vaccines, in fact coverage rates moved from values ranging from 95-97% in previous birth cohorts to 98.5 for poliomyelitis and hepatitis B and to 99 for diphtheria and tetanus in 2008 birth cohort [19]. Obviously available data on a single birth cohort are too limited to express a judgment of full validity of the Regional Law, therefore it will be necessary to continue to monitor levels of vaccination coverage and offer compliance in order to

Tab. I. Compliance to vaccines offer.

	Sept 2007	Mar 2008	Sept 2008	Mar 2009	Sept 2009	Mar 2010	Sept 2010	Mar 2011	Sept 2011
Hexavalent vaccine (dose 1)*	93.5	95.3	95.9	96.1	94.6	95.5	98.0	96.0	94.9
Hexavalent vaccine (dose 2)	94.4	94.8	95.2	96.9	96.9	96.4	96.0	97.3	97.2
Hexavalent vaccine (dose 3)	90.8	92.5	91.8	95.6	94.5	93.7	92.4	93.0	95.3
Pneumococcal vaccine (dose 1)	88.2	94.1	93.3	93.5	93.2	92.9	95.9	95.4	94.0
Pneumococcal vaccine (dose 2)	87.8	92.3	93.1	93.9	94.9	94.5	94.0	95.9	95.2
Pneumococcal vaccine (dose 3)	33.2	38.5	36.5	54.6	61.2	45.9	59.0	54.6	64.1
Meningococcal vaccine	89.2	91.7	89.1	93.7	90.9	87.2	90.1	90.1	92.2
Measles-Mumps-Rubella	72.3	75.2	78.3	84.3	84.3	78.4	83.0	82.6	84.9
Chickenpox	67.3	71.8	67.7	74.5	75.4	72.7	78.7	78.5	81.8

\* Hexavalent vaccine contains poliomyelitis, diphtheria, tetanus, pertussis, hepatitis B, H. influenzae B vaccines.

**Fig. 3.** Percentage of children at 24 months not vaccinated against polio according to motivation that led to non-vaccination (birth cohorts 2002-2008).



Not present includes domiciled abroad, nomads, homeless, not traceable.

highlight situations of deviation from expected value before warning situation occurs.

Opponents of this law consider that liberalization in the field of immunization poses a threat to consolidated practices of Public Health with the risk of decreasing vaccine coverage and increase the number of cases of infectious diseases easily preventable. However, first monitoring data are fully encouraging and demonstrate that there were no changes with regard to coverage, while acceptance of immunization offer remained constant for ex-mandatory and was even growing for ex-recommended vaccinations. In that regard, it should be noted that the legislative measure adopted by Veneto provides for a constant monitoring of vaccination coverage and compliance to invitation, a rigorous epidemiological surveillance of infectious diseases for which the requirement of vaccination is suspended, and immediate suspension of the Regional Law 7/2007 when coverage levels fall below the established threshold or in case of significant epidemiological events related to the disease for which the vaccination requirement is suspended.

The developed delivery system of vaccinations appears able to allow the suspension of mandatory vaccinations without risk to coverage, continuing to ensure a strong adhesion to all available vaccinations, as it is characterized by some essential elements: a strong degree of integration of vaccination services with pediatricians and family physicians; active and free offer of all vaccinations recognized as safe and effective; computerized immunization database that allows rapid recovery of non-adhesion to first call; the remarkable cultural

maturity reached by population that is constantly affected by actions of counseling and health education.

These observations support the conclusion that similar legislative measures can be adopted with comparable success, as advocated by NVP 2012-14, also in other Italian Regions, provided that they possess specific starting conditions: high levels of immunization coverage, ability to ensure an effective vaccination offer system, continuous monitoring of membership, a rapid recovery of any non-compliance based on dialogue and information.

The introduction of compulsory vaccination suspension law in Veneto Region has allowed experiencing a Public Health setting established on self-guided individual choice in making decisions regarding health, creating a modern and efficient vaccine service. Further research and reports are required to carefully value whether the choice between compulsory and voluntary vaccination takes effect on coverage rates.

In conclusion a healthcare system should promote and actively offer all vaccinations approved as safe, effective and with a positive public health impact. However decision about proposal for vaccine strategies should be elaborated in agreement with organizational features of vaccination services combined with traditional and cultural habits. Trust on health authorities will lead to more compliance with recommendations producing not only benefits for health of citizen but also enhancing their awareness on this issue and support the overall effectiveness of vaccination programs through the herd immunity effect.

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# Attitude and knowledge of Iranian female nurses about Human Papillomavirus infection and cervical cancer: a cross sectional survey

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## Key words

HPV • Nurses • Vaccine • Knowledge

## Summary

**Background and aim.** Human Papillomavirus (HPV) is one of the most widespread sexually transmitted diseases is highly related to cervical cancer in women. Cervical cancer's crude incidence rate in Iran is 6-8 per 100,000. The HPV vaccine provides a chance to considerably decrease the transmission of most types of HPV. The aim of this study was to evaluate awareness and knowledge of HPV infection and vaccines and to assess the attitude and approach toward these vaccines among female nurses at Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

**Materials and methods.** This cross-sectional, descriptive study was performed among 380 female nurses. Data were collected using a questionnaire consisted in demographic variables and questions on knowledge of participants about HPV infection, HPV vaccine and cervical cancer and also questions on attitude of nurses towards HPV vaccination. The validity and internal consistency of questionnaire was confirmed during experts con-

sents and pilot testing ( $\alpha = 0.79$ ). Data analysis was performed using SPSS15 using  $\chi^2$ -test or Fisher's exact test.

**Results.** Three hundred and eighty questionnaires were distributed and 357 female nurses completed and returned their questionnaires: Only one hundred and thirty-one of the nurses (36.7%) knew about HPV infection and how it can cause abnormal pap smear results. about 147 (41.2%) of the nurses stated they would want to be vaccinated. About 146 (40.9%) of respondents supported vaccination of preadolescent girls.

**Conclusion.** The results of this study confirm the lack of knowledge about HPV vaccine and its relation to cervical cancer and also the ways of this cancer prevention. Our study shows an urgent need to design similar studies in other regions of Iran and draw a broad estimation on knowledge of different target groups to make a national program to increase the knowledge of women on this matter and help to decrease the rate of cervical cancer in Iranian population.

## Introduction

HPV or The Human papillomavirus, is one of the most widespread sexually transmitted diseases [1, 2]. Over half of the sexually active women population is exposed to at least one type of HPV during their lifespan [2]. HPV infection can transpire in women of all age consortium, also higher rates of HPV infectivity are generally perceived in women 20-24 years old [3]. For the most part, genital HPV infections are asymptomatic, ephemeral, and resolve without no treatment spontaneously and cause no disorders or complaints. Genital HPV is classified as high risk which mostly is related to types 16 and 18 or low risk that is related to types 6 and 11, reflecting the potential risk to develop malignancy. The development of cervical intraepithelial neoplasia and cervical cancer is in correlation with a previous continual cervix uteri infection with a high risk HPV type [4]. HPV types 16 and 18 are the prime cause of 70% of all cervical cancers.

Cervical cancer transparency worldwide indicates that it is primarily a problem of low resource countries for the main reason of limited access to screening and treat-

ment facilities [1]. In countries with organized screening programs, cervical cancer incidence and mortality have significantly reduced. Cervical cancer is easily accessible to biopsy and also easily recognizable before development because of its long latent period, there for screening programs can be most effective, and there is an effective treatment in precursor disease [5].

Cervical cancer is the second common malignancy among women and the most frequent of gynecologic cancers worldwide [4]. Only in 2008 about 530,232 new cases were diagnosed, and 85.5% of these emerged in developing countries [6]. In developing countries, Cervical cancer is one of the chief public health issues and the leading cause of deaths related to cancer among women [7]. Cervical cancer's crude incidence rate in Iran is 6-8 per 100,000 [8].

It has been hoped that the on hand HPV vaccines will noticeably diminish the burden of cervical cancer and also other HPV-related diseases in developing countries. The HPV vaccine provides a chance to considerably decrease the transmission of both high risk types 16, 18 and low risk types 6, 11 and by doing so, not only reduce cervical cancer incidence and mortality rate,

but also the financial burden of diagnosis and treatment interventions [9]. Infections can be prevented for those with no prior exposure, there for administration have to take place in adolescents and before their sexual debut. The vaccine is expensive and not available to the public in low income countries [10-12].

Numerous studies, mainly in developed countries, have revealed that both health care providers and the general public have various knowledge of HPV infection and vaccines [13-21]. Nurses as a group of health care professionals can have important role in immunization programs, they because of their social situation can provide health education to the public and their knowledge of HPV infection and vaccine prevention will influence on the success of the immunization program against cervical cancer.

Based on our knowledge up to know there is no study on attitude and knowledge of health care professionals about HPV and its vaccination in Iran. This study evaluated the knowledge of HPV infection and vaccines and tried to determine the attitude and approach toward these vaccines among the female nurses at Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

## Materials and methods

This cross sectional descriptive study conducted among the nursing staff of Shahid Sdoughi teaching Hospital, Yazd, Iran. The study is approved by Research Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Assuming that 50% of the female nurses had sufficient knowledge of genital HPV infection, and with 95% confidence and 5% reliability about 300 needed participants were calculated for the study. The instrument of data collection was questionnaire covered information on socio demographic traits, on alertness and knowledge of HPV infections, cervical cancer, and HPV vaccines, and on approval of these vaccines. The questionnaire was developed in consultation with a health educator, two midwives, one gynecologist and an expert in questionnaire validation and its validity was confirmed. Also internal consistency of question-

naire was confirmed by piloting and calculating related  $\alpha$  ( $\alpha = 0.79$ ). The questionnaire was completed by hand throughout working hours by the participants. The purpose of the study was explicated to all nurses and their verbal consent was obtained before they were handed a pretested, structured, anonymous, self-administer questionnaire.

All registered information was transferred into SPSS-15 software using  $\chi^2$ -test or Fisher's exact tests. A p-value  $< 0.05$  was considered as statistically significant results.

## Results

### SOCIODEMOGRAPHIC CHARACTERISTICS

Out of the three hundred and eighty questionnaires that were disseminated, 357 female nurses completed and sent back their questionnaires. Two hundred and eighty one (78.7%) of the respondents were married while 76 (21.3%) were single. About 64 (17.9%) respondents were working in midwifery section and 293(82.1%) in other sections.

Only one hundred and thirty - one of the nurses (36.7%) knew about HPV infection and how it can cause abnormal Pap smear results. About 130 (36.5%) of them were aware that It is possible for the infected person to have no sign or symptoms. And only 37 (10.4%) of the nurses knew HPV may not cause herpetic lesions in men and women (Tab. I).

About 208(58.3%) of the nurses knew that HPV could be transmitted by sexual intercourse, while only 40 (11.2%) were aware that it could be passed on by skin-to-skin contact. The data of Table II revealed the knowledge of participants about HPV transmission.

147 (41.2%) of the nurses affirmed they would be inclined to be vaccinated, whereas 210 (58.8%) were reluctant to vaccination; reason given for unwillingness by 26.2% was inadequate knowledge of the HPV vaccines and 41.4% were concerned about the complication of the vaccine (Tab. III).

About 146 (40.9%) of respondents supported vaccination of preadolescent girls, while 209 (59.1%) did not. The ground on which to not advocate the HPV vacci-

Tab. I. Knowledge questions and responses of participants about HPV infection and its relation to cancer.

Do not know		Wrong		Correct		Responses Questions
%	N	%	N	%	N	
52.1	186	11.2	40	36.7	131	HPV infection can cause abnormal Pop smear results
47.3	169	16.2	58	36.5	130	It is possible that infected person has no sign and symptom
51.8	185	32.2	115	16	57	HPV infection resolve without treatment
46.8	167	42.8	153	10.4	37	HPV may not cause herpetic lesions in men and women
54.6	195	5.6	20	39.8	142	Some specific HPV genotypes (mostly16 and 18)can develop cervical cancer
62.5	223	15.7	56	21.8	78	HPV genotype that cause genital warts and cervical cancer is the same
64.7	231	18.5	66	16.8	60	HPV cannot cause cancer in men



**Tab. II.** Transmission questions and responses of participants about HPV infection and its relation to cancer.

Responses Questions	Correct		Wrong		Do not know	
	%	N	%	N	%	N
Blood component	120	33.6	61	17.1	176	49.3
Sexual relationship	208	58.3	13	3.6	136	38.1
Skin contact to genital	175	49	22	6.2	160	44.8
Using the toilet	79	22.1	111	31.1	167	46.8
Tear and saliva	157	44	29	8.1	171	47.9
Kissing	40	11.2	147	41.2	170	47.6

**Tab. III.** Questions about vaccine of HPV and responses of participants about HPV infection and its relation to cancer.

Responses Questions	Correct		Wrong		Do not know	
	N	%	N	%	N	%
How kind of vaccine of HPV is	50	14	0	0	307	86
HPV vaccine can prevent the cervix cancer	16	4.5	76	21.3	265	74.2
HPV vaccine can prevent genital warts	20	5.6	65	18.2	272	76.2
The women that injected vaccine has need to Pop smear	126	35.3	16	4.5	215	60.2
The best age for vaccination is?	70	19.6	60	16.8	227	63.6
Are you willing vaccination?	147	41.2	210	58.8	-	-
Do you vaccinate your girls	146	40.9	209	58.5	-	-

nation for preadolescent girls included (1) safety of the vaccine is not unverified; (2) the vaccine is expensive; and (3) the lack of enough knowledge about the vaccines and its potential complications. Only 16 (4.5%) of the respondents knew that vaccination of HPV can prevent cervix cancer and 20 (5.6%) knew that vaccination of HPV can prevent genital warts.

## Discussion

Awareness of HPV infection and vaccines was moderately low amongst nurses in this study. Despite the understanding and familiarity of cervical cancer and HPV infection, a relatively low proportion (36.7%) knew about the correlation between HPV infection and cervical cancer. In other parallel studies 78.5% of Greek, 71% of New Zealander, and 81.8% Thai nurses were aware of this correlation [21-24]. This data exhibits the inadequate knowledge of nurses in our study and the necessity of increasing this knowledge.

A number of studies display that knowledge of HPV infection is higher in countries with an existing nationwide HPV education programs. These programs caused an enhanced alertness and better knowledge and understanding of HPV infection and associated diseases among health care providers and the general public.

In this Iranian study, only a 16 (4.5%) of the nurses knew they were for the prevention of cervical cancer. This is relatively low as opposed to the 39.1% in Thailand [24]. The nominal familiarity of the HPV vaccine among the nurses in this Iranian study may be due to the lack of education programs about cervical cancer and HPV infection in Iran. The important notable is-

sue is that our participants we nurses and reasonably they passed some lessons about viral infections and malignancies. In fact our participants were previously educated during their graduation courses but even in such group of people we found lack of knowledge. This shows needs for continues educational programs for all target groups as most of our previously educated respondents were failed to answer knowledge questions of our study.

About 147 (41.2%) of the female nurses gave consent to vaccination. These results are lower than those obtained from nurses in the Thai and Nigerian studies [24, 25]. 146 (40.9%) of the nurses were also amenable to propose the HPV vaccines for preadolescent girls. These findings were lower than what was stated in other recent studies [13, 14, 19, 21, 25, 26]. These studies initiated that despite the overall lack of knowledge about HPV infection and other related diseases, the public interest in the HPV vaccination was significant. Studies also display that the main predictors of providers' intent to recommend HPV vaccination are endorsed by specialized organizations and provider of knowledge and approach toward HPV vaccination [23, 26, 27]. Furthermore, the Authors point out that the nurses who gave their consent to be vaccinated were also the more likely to suggest the vaccine for preadolescent girls.

The nurses' justification for not consenting to the HPV vaccines or promoting it for preadolescent girls was the information inadequacy about the effectiveness and safety of the vaccines and also the high cost of the vaccine. In other studies, these factors were also acknowledged as difficulties to an effectual HPV immunization [14, 28-30]. virtually all the nurses sought to obtain more information about the vaccines.

## Conclusions

The results of this study confirm the lack of nurses' knowledge about HPV vaccine and its relation to cervical cancer and also the ways of this cancer prevention. Considering with this fact that nurses are educated previously during graduation courses and their low level of knowledge about HPV infection and vaccine, we recommend contentious educational programs for health care staffs as they are one of the most sources of public to get information about diseases. Our study shows an urgent need to design similar studies in other regions of Iran and draw a broad estimation on knowledge of different

target groups to make a national program to increase the knowledge of women on this matter and help to decrease the rate of cervical cancer in Iranian population.

## LIMITATIONS

The relatively small sample size and it being as self-administer, are the probable confines of this study.

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