Volume 15 n. 1/4 Gennaio/Dicembre 2010

SOCIETÀ ITALIANA DI MEDICINA TROPICALE

Giornale Italiano di MEDICINA TROPICALE

Italian Journal of TROPICAL MEDICINE

RIVISTA UFFICIALE DELLA SOCIETÀ ITALIANA DI MEDICINA TROPICALE

ISSN 0394-3445

Giornale Italiano di Medicina Tropicale • Volume 15 • n. 1/4 Gennaio/Dicembre 2010

Giornale Italiano di Medicina Tropicale

Italian Journal of Tropical Medicine

Rivista ufficiale della Società Italiana di Medicina Tropicale
Official Journal of the Italian Society of Tropical Medicine

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Periodico trimestrale registrato al n. 499/87 del 22 settembre 1987 del Registro del Tribunale di Roma.
Proprietà: Società Italiana di Medicina Tropicale
***Direttore Responsabile*:** Giancarlo Majori
Composizione e impaginazione: Maria Grazia Bedetti
Stampa: Centrostampa De Vittoria S.r.l., Via degli Aurunci, 19 - 00185 Roma

Finito di stampare nel mese di dicembre 2010

Giornale Italiano di Medicina Tropicale
Italian Journal of Tropical Medicine

VOLUME 15 NUMERO 1-4, GENNAIO - DICEMBRE 2010
VOLUME 15 NO 1-4, JANUARY - DECEMBER 2010

Ethical criteria in clinical research in developing countries: is there a global standard?

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Summary - Clinical researchers in developing countries face multiple challenges related to contextual constraints, poor regulation and vulnerability of trials' subjects. The World Health Organization issued in 1995 its Good Clinical Practices (GCP) Guidelines, setting globally applicable standards for clinical trials. Non-compliance with GCP principles leaves room for misconduct and abuse, while a rigid interpretation of GCP processes and procedures may unnecessarily increase the research costs and even prevent research relevant to public health from being carried out.
Ethical principles and scientific standards governing research are universal and should be adopted everywhere, to ensure persons' protection and data's reliability, while avoiding any North-South ethical divide. However, principles should be translated into simple and effective processes and procedures, which ensure quality of the research and subjects' protection, without putting unnecessary obstacles to public-health oriented research. It is time to "reinvent" GCP, by updating the 1995 WHO Guidelines in light of the 15-year experience of worldwide implementation. The revision should include old and new stakeholders (including academic institutions from the South and the North, NGOs, public-private partnerships, donors, patients associations etc.) and could, by making clearer distinction between essential and procedural requirements, help researchers and sponsors to design new patient-centered tools and practices.

Key words: ethics, standards, clinical research, developing countries

INTRODUCTION

Clinical research has been a keystone in solving many public health problems faced by the world population. As reported by the Global Forum for Health Research (2004), of the estimated US$ 56 billion spent annually on medical research by the global community, at least 90% is spent on the health needs of the richest (10% of the world's population), while only 10% addresses the needs of the remaining 90% of the world's population. The unequal distribution is linked to the poor economy in developing countries, resulting in lack of adequate financial and human resources. Nonetheless, the number of clinical trials carried out in the South has significantly increased over the last years. The increase is partly due to a trend to move the research to countries with more favourable costs, less rigorous regulations and greater availability of patients and medication-naïve patients (Rehnquist, 2001; The European Group on Ethics in Science and New Technologies to the European Commission, 2003; Wemos and European Parliament, 2007; Schipper and Weyzig, 2008) and partly to an increase of public health-oriented studies, addressing major unanswered health problems.
Clinical researchers face many challenges in resource-limited contexts, including contextual constraints (transport, internet connection, etc.), poor regulation, and vulnerability of the trials' subjects, due to socio-economical factors, illiteracy, marginalization or exclusion.
The World Health Organization (WHO) has developed and published almost 15 years ago its Guidelines for Good Clinical Practices (GCP) (World Health Organization, 1995), for setting globally applicable standards for the conduct of trials on pharmaceutical products on human subjects. "Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with

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Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

the principles enunciated in the Declaration of Helsinki (World Medical Association, 2008) and other internationally recognized ethical guidelines, and ensures the integrity of clinical research data" (World Health Organization, 2002).

The WHO Guidelines comprises **principles**, **processes** and **procedures**.

The **principles** are summarized in chapter 1.2 of the Declaration of Helsinki: "All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki. Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) and non-maleficence (doing no harm) as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS, 2002) or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles".

The **process** and **procedures** concern the structure of the protocol, the concrete measures to be taken for the protection of trials' subjects, the responsibilities of the Investigator, of the Sponsor and of the Monitor, the monitoring of safety, the record-keeping and handling of data, the statistics and calculations, the handling and accountability of pharmaceutical products, the role of the drug regulatory authority, the quality assurance and some additional considerations for multi-centre trials.

The WHO recommends that these principles, processes and procedures be applied to all clinical research. It has been widely demonstrated that non-compliance with GCP principles leaves room for misconduct, fraud and abuse, especially when trials are carried out in the South for convenience reasons (Schipper and Weyzig, 2008a; Wemos, 2008; Louwenberg, 2008). However, a rigid interpretation of GCP processes and procedures may unnecessarily increase the costs of the research (White, 2006; Stewart *et al.,* 2008). In developing countries, where resources and time are limited, the emphasis on processes and procedures may create competition between medical research and patient care, and some think that it may even prevent to carry out non-commercial research relevant to public health.

To analyze the tension between the two extremes of "GCP relaxation" and "GCP rigidity", a debate took place on 8th September 2009 during the 6th European Conference of Tropical Medicine: is there a global standard for clinical research? Should standards be adapted in developing countries? How to encourage research while preventing the exploitation of vulnerable individuals or groups?

Five "debate questions" (Tab. 1) where addressed by Professor Nick White and by Dr. Lumuli Mbonile, and discussed with the moderator (Raffaella Ravinetto) and the audience. The following chapters reflect the debate and discussion, trying to be as inclusive as possible of the different positions.

Question 1. Research standards

Clinical research is premised on two fundamental moral commitments: to improve human welfare by advancing scientific knowledge and understanding of disease, and to preserve and protect the dignity and health interests of the research participants. The potential risk of harm, as well as evidence that misconduct and fraud occurred both in the North and in the South of the world, led to agreement that sound, universal ethical standards are needed, irrespective of the geographic and economic setting where research is undertaken.

On the one hand, we were reminded that research standards, as expressed in the principles of the WHO GCP guidelines, were derived from the rule of common morality, which is applicable to all persons in all places and which, together with moral characteristics traits or virtues, is universal. Since common morality rules constitute the building blocks of research ethics and of GCP, the GCP principles should be applicable and should be adopted everywhere. GCP processes and procedures are derived from the principles, and their implementation is necessary to try and ensure *a priori* that all the patients worldwide are protected in the same way, that all the research is of sound scientific quality and that all research data are fully reliable:

Table 1 - The five debate's questions

1. Research standards: should WHO GCP standards be adapted for clinical research that addresses relevant health questions in developing countries?
2. The role of funding agencies: should researchers working in externally-funded projects in developing countries advocate for an increase of research budgets to better cover GCP-requirements?
3. Research standards in emergency settings: should exemptions to GCP requirements be considered?
4. Ethical review of "externally sponsored trials": should we solely focus on strengthening the ethical review in developing countries, or should we build on complementary mechanisms, based on North-South double ethical review?
5. Standard of care: is it acceptable to use different standards concerning the choice of a placebo control, in developed versus developing countries?

processes such as external monitoring, verification of source data and documentation of the appropriate use of investigational medicinal products are thus essential to ensure these general principles are respected.

From another perspective, however, although the principles of common morality are generalisable, the processes and procedures are not, because they are derivative and strongly influenced by cultural and contextual elements. From this perspective, it was noted that most GCP guidelines have been issued by developed countries (International Conference of Harmonization, 1996), or are based on the experience of the industry-sponsored research, so they reflect the experiences, objectives, financial capability and skills of commercial research. This applies to some extent also to the WHO GCP Guidelines, issued in 1995: the text was developed in consultation with national drug regulatory authorities within WHO Member States, and discussed during two informal consultations attended by representatives of the WHO, the International Union of Pharmacology, Universities from Indonesia, Denmark, Zambia, Brazil and China, pharmaceutical agencies from Japan, the USA, Russia and Sweden, the International Federation of Pharmaceutical Manufacturers Association and a pharmaceutical industry (Ciba-Geigy). The recommendations are very similar to those applied by industry to pre-registration clinical trials, and they require a level of human resources and management detail that is not based on a risk-approach and goes beyond the capacities of most academic and non-commercial groups.

From this perspective, several formal requirements, in addition to being complicated and expensive, are of uncertain value, because too often the focus is put on the processes rather than on the persons. For instance, external monitoring often focuses exclusively on the examination of the CRF and related documents (checklist approach), without looking at the context of the clinical sites and at the approach to the patient. The informed consent is mainly seen as a signature (verification of a formal requirement) rather than a relational process. The ethical and regulatory review themselves may focus on specific technical aspects highlighted in GCP (e.g., informed consent, investigational medicinal products etc.) rather than on a comprehensive review of the protocols, so that they often end up overlooking major scientific or methodological weaknesses in the research.

So on one hand, we face a moral requirement to ensure universal enforcement of universal research ethics principles, so as to avoid improperly designed trials, to prevent the exploitation of individuals and groups, to promote pertinent research in countries with poor resources and to avoid any North-South ethical divide. The increase in costs linked to compliance with guidelines is, in this perspective, largely justified by the benefits.

On the other hand, we face a moral requirement to translate GCP principles into simple and effective processes and procedures: simplicity should be seen as a guiding value, for designing effective rules that ensure quality of the research and subjects' protection, without putting unnecessary obstacles to public-health oriented clinical research carried out for the benefit of the Southern populations.

A balance must be found between the two extremes of rigidity and relaxation, which both produce inequalities. There was agreement that a revision of the 1995 WHO GCP Guidelines, while leaving principles unchanged, was needed. This could act as a basis for the design of new patient-centered tools and practices.

Question 2. The role of funding agencies

The WHO GCP guidelines, published in 1995, define the sponsor as "an individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial", while it does not explicitly mention the role of the Donors, taking it for granted that each sponsor funds its own trial and manages its own budget. This is the case in industry-sponsored trials. However, a great deal of the research programs carried out by non-commercial sponsors, NGOs, academic organizations, etc., to address the health problems of populations of developing countries, are funded by external Donors.

Full compliance with GCP incurs large costs. As a result in externally-funded clinical trials it is the funding policy of the Donor/s that concretely sets the "GCP level". For instance, external monitoring is requested by GCP for ensuring subjects' protection and reliability of data: however, quality external monitoring implies additional costs, which should be covered by the Donor, which is generally from a Northern country or institution. The same applies to other tools and process which should improve the patients' protection (e.g., the no-fault policy insurance for clinical trials) or the quality and reliability of research data (e.g. validation of databases). Are the research budgets generally sufficient to cover all the "quality costs"?

On one hand, it was felt that researchers working in externally-funded projects in developing countries should advocate for an increase of research budgets, to cover GCP-requirements more comprehensively. The increase in research-related costs would be justified by important benefits: would maximize the participants' protection, ensure the quality of data, prevent misconduct, improve collaborative research

tools and increase the research awareness among participants in developing countries. From a North-South perspective, in addition, funding policies should always ensure that the same research standards are applied in the country of the donor (developed countries) and in the research countries (developing countries).
On the other hand, the implementation of GCP principles should give priority to essential requirements over formal and procedural aspects. If too much attention is given to the process and insufficient attention is given to the patient and his/her context, the increase of the "GCP budget" could mean that financial resources are diverted from essential to non-essential requirements. In this view, the donors should support what is needed to ensure optimal design, best care of the patients, ethical conduct and credible results, without diverting money to burdensome, complicate and non-essential activities.
A balance should be achieved between universal standards and contextualized practices and tools, without ever losing the focus on the patient.

Question 3. Research standards in emergency settings

Increasingly, international and nongovernmental organizations providing emergency medical care and humanitarian assistance to vulnerable populations are turning into producers of health research, which range from simple health surveys or interview studies, to complex clinical trials (The PLOs Medicine Editors, 2009; Priotto *et al*., 2008; Priotto *et al*., 2009). This research is of paramount importance to address the specific problems of populations living in extremely poor and unstable settings, in conflict and in disaster situations. However, there is undoubtedly a huge tension between the ideal setting for medical research, which requires stable and controlled operating environment, and emergency contexts. Situations marked by violence and insecurity, in particular, are often characterized by acute ethical dilemmas: power unbalance versus informed consent process; signed informed consent versus confidentiality and security; lack of formal ethical review structures versus need to intervene quickly (e.g. in case of epidemics); limited political and institutional recognition of ethical issues; competing interests and limitations in research skills and practice (Schopper *et al*., 2009; Zwi *et al*., 2006).
Full compliance with GCP formal processes and procedures may be impossible: should we then give up the possibility of carrying out research, so further neglecting the health needs of these vulnerable populations? Or should exemptions to GCP requirements (e.g., written informed consent, preliminary ethical approval, external monitoring, etc.) be considered in emergency contexts?
On one hand, it was noted that even if the general ethical principles are universal, there are specific ethical challenges that researchers encounter in emergencies. An interesting example comes from a case study presented by Richard Black of the University of Sussex (Reed, 2002). In Liberia, two codes of conduct for humanitarian action were developed during the emergency: the Principles Humanitarian Operations (PPHO), a United Nations initiative, and the Joint Plan of Operations (JPO), initiated by the NGOs. The PPHO was focused on such issues as impartiality, neutrality, independence, informed consent and the targeting of aid, because of a concern that aid was sustaining or legitimizing armed factions. The JPO was instituted after the April 1996 looting of aid and ransacking of NGO offices by armed factions; its focus was on minimum targeted lifesaving activities. The two ethical codes tended to place limits on research and operations in Liberia, but Black argued that the very process of establishing codes was useful, because it created a dialogue between donors and agencies about ethics. Yet there was poor coordination among agencies.
Redundancy and overlap are a common problem in emergency settings, with an accumulation of similar studies without any coordination among research teams (is it ethical to approach again the same population to collect similar data if prior data remain unused?). From this experience, we can draw the lesson that establishing rules remains crucial in emergency settings, where the lack of regulation creates or aggravates specific ethical problems.
Thus, the procedures derived from research ethics principles should not be systematically waived in emergency contexts. For instance, informed consent is essentially a relational process, not a one-time signature; the "formal" requirement of signature should be maintained, unless an exemption is needed for protecting the persons and/or when the research is at very low risk (e.g., surveillance in outbreaks). Waivers should only be based on the patients' needs and benefits. In addition, whenever possible, the study populations should be involved in designing or at least approving the alternative procedures: representatives of the community could be members of the independent review committees, and research subjects could be involved in the research process (observation, focus group, etc).
On the other hand, we were reminded that in emergency situations the distinction between essential requirements (which have an actual added value in terms of persons' protection and research quality) and non-essential requirements (procedural requirements, without an added value), is more crucial than ever. The translation of principles into practices and

tools should have the primary objective of protecting the persons and maximizing the value of the research, without putting unnecessary obstacles to pertinent and useful research.
"Excellent studies can be very simple": The benefits and risks should be carefully weighed on a case-by-case basis, in terms of harm reduction (for those who have already suffered harm and/or are at greater risk of harm) and of life protection. Delaying or preventing useful research may be as harmful to people as misconduct and fraud in research.

Question 4. Ethical review of "externally sponsored trials"
The term *externally sponsored research* refers to researches undertaken in a host country, but sponsored, financed or wholly or partly carried out by an external international or national organization or pharmaceutical company, with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country. Most donors are from the rich and technologically-advanced nations, while developing countries provides research sites and participants and, increasingly, medical and scientific knowledge.
The collaboration between developed and developing countries needs a balanced harmonization strategy, and this also concerns the ethical clearance process. According to the CIOMS Guidelines (Council for International Organizations of Medical Sciences, 2002), "an external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards". However, many developing countries lack an effective ethical review system: according recent studies, the 45% of US-funded studies conducted in developing countries in 2004 did not undergo technical, scientific or ethical review (Hyder *et al*., 2004) and 70% of developed countries lack ethical review capacity (Milford *et al*., 2006). Given that the overall funds for clinical research and research capacity strengthening in developing countries is still insufficient compared to global needs, which priorities should be set? Strengthening the ethical review in developing countries, or building complementary mechanisms, based on North-South double ethical review?
On one side, it was noted that research capacity building is still fragmented: the "developed" and the "developing" blocks have created their own research priorities, review mechanisms and guidelines, rather than promoting collaboration. The North-South divide is especially evident for ethical review process and procedures: cultural diversities and standards of care have been used for many decades as an excuse for insufficient global collaboration on ethical mechanisms, raising a paradoxical question as to which to promote between culture and good health. In this perspective, the North-South collaboration on ethical review of trials is crucial and it should go well beyond the adoption of common guidelines for establishing and training Ethics Committees (ECs): a communication link should be created between ECs in the North and in the South, to benefit from the complementarity of perspectives (mutual learning), and to contribute to overcome the North-South gap in research capabilities.
On the other side, it was reminded that the relevance of North-South collaboration should not divert the focus from the "local" ethical approval, which should never be replaced by external expertise. In this view, investments should primarily be done in strengthening the review capacities in Southern countries (TDR/WHO, 2000; GCP/WHO, 2003).
From both perspectives (focus on North-South collaboration vs. focus on the quality of the local ethical approval), it appears that ethical review everywhere needs to be supported by appropriate quality assurance mechanisms encompassing the ethical, methodological and scientific points of views (bad science in clinical research is *per se* unethical). This is crucial to ensure that standards are upheld, and to avoid, as far as possible, that biased or unreasonable reviews prevent good research or endorse bad research.

Question 5. Standard of care: the use of placebo.
According to the WHO GCP, "the current revision of the Declaration of Helsinki is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials". The 2008 version of the Helsinki Declaration states that "the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option".

This wording leaves room for different interpretations and for translation in different practices. In addition, it does not clearly address the question of whether it is acceptable to use different standards concerning the choice of a placebo control, especially in developing countries, where the different standards of practice and care create quite specific questions (Lie *et al*., 2004; Bhutta, 2004; Shapiro and Benatar, 2005; Wendler *et al*., 2004; Angell, 1997; Lurie and Wolfe, 1997).

In general, exploitative studies that do not address the needs of the population of the host country are not acceptable in the frame of the Helsinki Declaration. On October 27th, 2008, however, the US FDA formally discontinued its reliance on the Declaration and substituted the ICH GCP. According to some comments, the FDA decision may have been motivated by the differences between these documents relating to the use of placebo controls in trials (Kimmelman *et al*., 2009; Goodyear *et al*., 2009).

Placebo controls are ethically justifiable only if they are supported by sound methodological considerations and when their use doesn't expose research participants to excessive risks of harm. In developing countries, in particular, studies which could improve health care by providing evidence of benefit compared with currently available best practice should be facilitated, and under some circumstances the use of placebo may be justified (Onder, 2005).

The risk for the participants can never be entirely eliminated: so, the risk- benefit analysis will always be complex, and should include such elements as the best available standard in the host country, the post-trial availability and affordability of the study drug, the inherent conflict between clinical research versus clinical practices, etc.

CONCLUSIONS

Ethical principles and scientific standards governing clinical research are universal, and should be adopted everywhere, to ensure protection of persons, quality of the research and reliability of data, while avoiding any North-South ethical divide.

However, the principles and standards as stated in GCP guidelines are translated in processes and procedures, which are influenced by the contexts where the guidelines are issued. In addition, they are further translated in national laws, practices and tools, which should be adapted to contextual constraints, so as to avoid exploitation and bad practices on one hand, and to encourage public health-oriented clinical research on the other hand.

It is time to "reinvent" GCP, by updating the 1995 WHO Guidelines, in light of the 15-year experience of worldwide implementation. Where possible, the updated Guidelines should be simplified and clarified, by taking into account the specificities of different contexts and by building a risk-based approach which goes beyond the traditional phase I-V classification.

The revision process should include all the "old" stakeholders and "new" stakeholders (academic institutions from the South and the North, NGOs, public-private partnerships, donors, patients associations, etc.) and could, by making clearer distinction between essential and procedural requirements, help researchers and sponsors to design new patient-centered tools and practices.

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Health of Palestine Refugees in the Eastern Mediterranean: Determinants and Challenges

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Summary - Since 1949, Palestine refugees have become the most numerous refugee group in the World. The humanitarian UN Agency UNRWA has been working for the past 60 years to protect them from the consequences of socio economic hardship providing primary health care, education and social relief in Jordan, Lebanon, West Bank, Gaza Strip and Syria. In this article the authors provide an overview of the determinants health and health status of Palestine refugees in the Eastern Mediterranean since the establishment of the Agency discussing the challenges that they still face.

Salute dei rifugiati Palestinesi nel Mediterraneo: determinanti, barriere e opportunità.
Riassunto: Dal 1949, i rifugiati Palestinesi sono diventati il singolo gruppo di rifugiati più numeroso al mondo. L'agenzia delle Nazioni Unite UNRWA da 60 anni opera per proteggere i rifugiati Palestinesi dalle conseguenze delle difficoltà economiche e sociali a cui sono esposti fornendo assistenza sanitaria, scuole e sostegno sociale in Giordania, Libano, Cisgiordania, Striscia di Gaza e Siria. In questo articolo gli autori descrivono i determinanti della salute e come è cambiato il profilo sanitario dei rifugiati Palestinesi dall'inizio delle attività dell'Agenzia discutendo gli ostacoli cui vanno incontro oggi.

Key words: Palestine, refugees, health, Eastern Mediterranean

INTRODUCTION

In the aftermath of the 1948 Arab-Israeli war some 800,000 Palestinians traumatised by the violence of the conflict and the loss of their ancestral homes were the first beneficiaries of the newly established United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA). For the last 60 years UNRWA has been providing health services and monitoring the health status of a growing population of Palestine Refugees in Jordan, Lebanon, Syria, West Bank and the Gaza Strip. UNRWA's health programme has gradually become a network of 138 primary health care clinics serviced by 3000 health care workers, including 430 doctors, who deliver comprehensive primary health care services free of charge. In addition the Agency provides secondary care either directly or by contracting external facilities. Although UNRWA started operating in a classic post-conflict situation, since then the socio economic conditions of its beneficiaries have diversified according to the political and economic situation of their host countries, including the recognition of refugee status and the level of access to Government services. Refugees are therefore a diverse population with diverse needs and health priorities. On top of this, the chronically volatile security context in this part of the Middle East has obliged UNRWA to adopt a dynamic two tired approach balancing emergency relief with human development according to the situation on the ground. It has made UNRWA an extremely adaptable Agency capable of guaranteeing the continuity of its services though closure regimes as well as full blown conflicts (UNRWA, 2008).

Palestine refugees today

Today almost five million people are registered with UNRWA, a rapidly growing, young population with high fertility rates and increasing life expectancies. Across UNRWA's area of operation 38.8% of refugees are children below 18 years of age. The demographic profile of the registered Palestine refugees in Lebanon, Jordan and Syria is comparable to that of other countries of the Near East, conversely in the occupied Palestinian territory (oPt), particularly in the Gaza Strip, there is a higher pro-

Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

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portion of children under 15 and the fertility rate is higher both considering UNRWA and National estimates. The UNRWA calculated 2008 dependency ratio, measured as the proportion of the population below 15 and above 65 years of age, was almost 90% in the Gaza Strip (Tab. 1). This implies that the economic burden on family units is particularly high, even not taking into account the contextually high unemployment rates and worsening poverty levels.

The environmental health conditions in which Palestine refugees were living in 1949 were appalling. Malnutrition was rife and morbidity and mortality rates from air and water-borne infections and communicable diseases such as malaria, gastroenteritis, tuberculosis and trachoma were very high. UNRWA not only provided health care services but worked to improve water and sanitation in the newly established refugee camps, fought malnutrition and was particularly innovative in the fight against communicable diseases. A highly effective malaria eradication programme in the Jordan Valley was complemented by an expanded programme of immunization reaching the high level of immunization coverage it has maintained today.

Health status

Health indicators for Palestine Refugees residing outside the occupied Palestinian territory (oPt) are overall comparable to those of their host countries. In the oPt however the Gaza Strip compares unfavourably with the West Bank although they share the same healthcare providers and have comparable populations. This finding is consistent whether considering data for the whole Gazan population (Palestine National Authority/WHO) or refugees (UNRWA). The Gaza Strip has consistently higher infant and maternal mortality rates, a lower life expectancy, and reports higher levels of undernutrition and micro-nutrient deficiency.

Elevated access to health services (66% of registered refugees accessed UNRWA health facilities in 2008) and the high motivation and quality of its staff are among the factors that have allowed UNRWA to contribute in improving the health status of its beneficiaries. The high coverage of UNRWA Primary Health Care services however has a different meaning than the same finding in a Country. It is an expression of an increasing economic vulnerability and/or limitation to health access that are making Palestine refugees more and more dependent on the Agency as their sole health care provider. There has been a dramatic increase in the coverage of UNRWA mother and child health services since 1990 that tends to exceed coverage rates reported by host countries in particular in the Gaza Strip and Lebanon where the socio-economic conditions of Palestine Refugees are the harshest. Conversely within the oPts, coverage is lower in the West Bank, again underlining the difference between these refugee groups even though they both have full access to Palestinian National Authority health services (UNRWA, 2009).

MDG targets for infant mortality have been reached by UNRWA in Jordan, Lebanon and the West Bank. Rates are in line with host countries except in Syria that consistently reports lower mortality figures. This could be related to the different sampling of the surveys as Palestine refugees in Syria are only 2.3% of the population whereas they constitute between 11.4 and 71.5% of the population in other countries making an overlapping of survey results more likely.

Table 1 – Socio economic indicators, oPt, Israel and Palestine Refugees, 2008-9.

Indicator	Year	Gaza	Gaza (Palestine refugees)	West Bank*	West Bank (Palestine refugees)	Israel*
Population	2008-2009	1,551,859	1,073,303	2,461,267**	762,820	7,233,701
Life expectancy (years)	2009	73.42	NA	74.54	NA	80.73
Total fertility rate children born/woman	2005-2009	5.03	4.6	3.22	3.1	2.75
GDP - real growth rate	2008	0.8%	NA	0.8%	NA	3.9%
Unemployment rate	2008	41.3%	NA	16.3%	NA	6.1%
Population below poverty line	2005-7	80%	NA	46%	NA	21.6%#
Infant mortality (deaths/1,000 live births)	2005-2006***	24 (oPt)	20.2	24 (oPt)	19.5	4.0
	2009*	18.35		15.96		4.22

*source CIA estimates (CIA world fact book https://www.cia.gov/library/publications/the-world-factbook/); #the poverty line for Israel is $7.30 per person per day; **in addition to these there are about 187,000 Israeli settlers in the West Bank and fewer than 177,000 in East Jerusalem; ***source UNRWA Infant mortality survey 2008 and MDG official website.

There are signs of a stabilization of infant mortality trends especially observing the preliminary results of the UNRWA 2008 survey for Jordan, West Bank and Syria (Fig. 1). This was expected as post-delivery and neonatal assistance is mainly provided by public health care services and, therefore, infant mortality rates cannot be expected to decrease significatively below national levels until health infrastructure and human resource development allows secondary and tertiary facilities to reduce prematurity, low birth weight and malformation related deaths, that are the leading causes of infant mortality today (UNRWA, 2009).

Vaccine-preventable diseases are well under control in all UNRWA's areas of operation and MDG monitored measles immunization coverage is consistently above 95% and in line with national rates. The decline in infectious disease incidence is a generalized trend in the region however diseases associated with poor environmental health, such as viral hepatitis and enteric fevers, are still a public health threat reflecting local endemicity patterns.

The global change in eating habits and lifestyles is also leading to higher caloric intakes and physical inactivity in Palestine refugees. However, this higher caloric intake is not associated with mitigation of existing nutritional deficiencies, which leads to a new and perhaps more unsettling kind of malnutrition, in which an excessive caloric intake, in the form of fat and carbohydrates, accompanies a persistent lack of micronutrients. Obesity is highly prevalent, reaching 53.7% in women in Jordan, while the lowest prevalence is found in Lebanon (men 23.6%, women 40.6%) (Mousa *et al*., 2010). Conversely, although severe under-nutrition as reported in the 1950s and 1960s is no longer highly prevalent, moderate stunting is still a problem among children under five in the oPt and in 2006 prevalence was placed at 12.4% in the Gaza Strip, as opposed to 7.9% in the West Bank. This highlights again the difference between these two refugee groups (PCBS, 2008). Iron-deficiency anaemia and vitamin-A deficiencies remain severe public-health problems among Palestine Refugees in the Near East. In Lebanon, the prevalence of anaemia among children under three years of age in 2004 was 33.4%, which makes it the highest in Palestine refugees who live outside the occupied Palestinian territory (28.4% in Jordan and 17.2% in Syria). In the same survey, the prevalence of anaemia in West Bank and the Gaza Strip was higher (34.3% and 54.7%, respectively) (UNRWA, 2004) and a pejorative trend was highlighted in both Fields in 2006 with a prevalence of 37.1% in the West Bank and 57.5% in the Gaza Strip (UNRWA, 2007).

Mental disorders, related to the chronically harsh

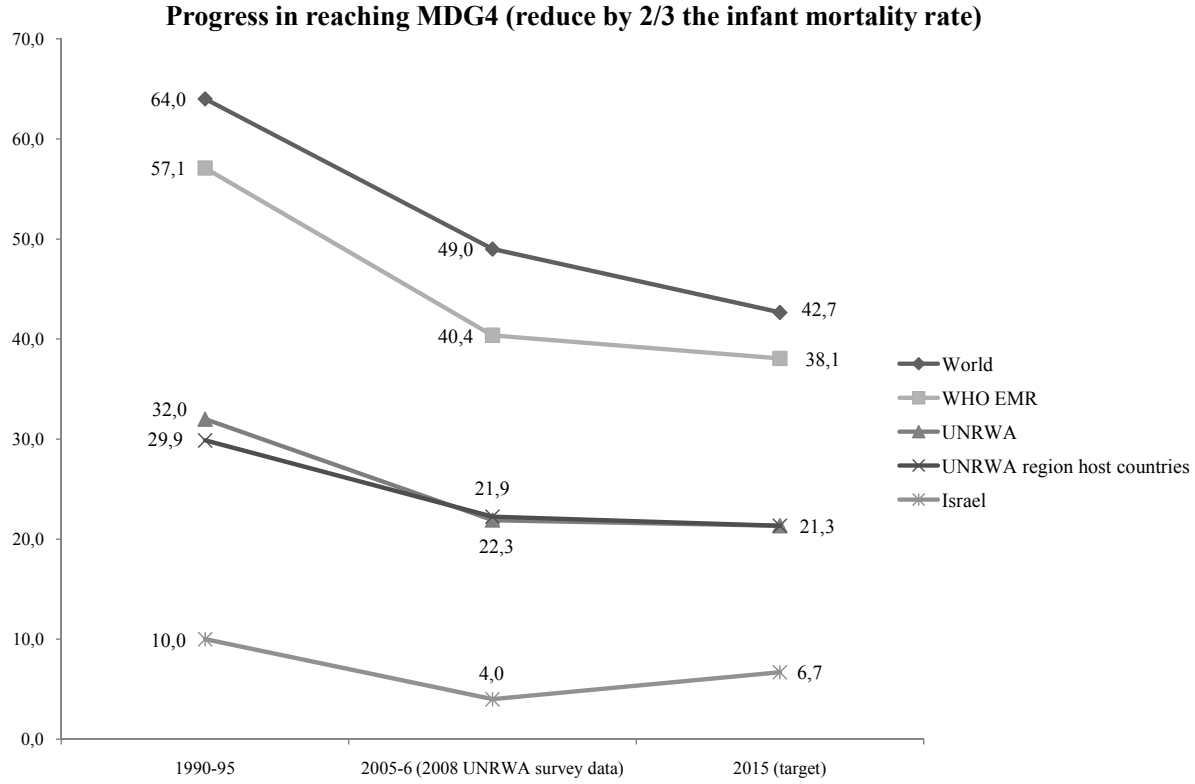

Figure 1 – Progress in reaching MDG4 (reduce by 2/3 the infant mortality rate), World, Eastern Mediterranean, UNRWA region and Israel (sources: www.unstats.un.org/unsd/mdg and UNRWA 2008 infant mortality survey).

living conditions and long-term political instability, violence, and uncertainty are becoming a public-health concern. In Lebanon, 19.5% of Palestine refugee adolescents suffer from mental distress and 30.4% of women in the same refugee camps reported mental distress (United Medical Group for Lebanon, 2006). Post-traumatic stress and other psychological and behavioural disorders, a documented consequence of exposure to traumatic events, are an emerging health priority also in the oPt. The chronically harsh living conditions of Palestine refugees coupled with long-term political instability, violence and uncertainty are taking their toll, in particular on children and adolescents. Since September 2000, the Palestinian population has been affected by demolition of homes, siege, closures, curfews that caused a spiralling poverty among the population. The Barrier has divided families and limited access to schools, work and basic services, contributing to increasing the relevance of mental health issues notably among Palestinian youth. Successive studies have highlighted the short- and long- term negative effects of the ongoing conflict on Palestinian children and youth, including fear, episodes of bedwetting, difficulty in concentrating, eating and sleeping disorders, irritability, and increased anti-social behaviour during adolescence and neurotic problems during adulthood. Palestinian students in Ramallah experience among the lowest levels self-satisfaction in the World (Giacaman *et al*., 2009) and according to screening activities conducted by UNRWA in schools in the Gaza Strip, a quarter of Palestinian students is estimated to be affected by symptoms of psychological disorders related to stress and trauma. During 2008, the most common disorders treated by the UNRWA mental health programme in the Gaza Strip were aggressive behaviour (17%), family problems (11%) and lack of motivation (8%) (Sabatinelli, 2009).

Determinants and challenges

The political and economic situation, the recognition of refugee status, and the level and possibility of access to governmental services in the hosting countries are the main determinants of the health status of Palestinian refugees living outside the oPt while the worsening socio-economic hardship due to the progressive fragmentation of the West Bank and the isolation of the Gaza Strip are among the main determinants identifiable within the oPt. These multiple factors are responsible for the high levels of poverty, for the level of access inequity to health and heath care services and more in general for the consequences of chronic social discrimination. On top of this, conflicts in particular in Lebanon and more recently in the Gaza Strip have brought a rapid deterioration of their living conditions with increased mortality and morbidity, loss of infrastructure and increased needs for specific health services such as rehabilitation and mental health.

Lebanon currently hosts over 400,000 Palestine refugees (UNRWA, 2008a), of whom over 50% live in refugee camps. Refugees in Lebanon are ineligible for the state's social services, including health care, and are exposed to recurrent episodes of violence. The employment restrictions faced by refugees, combined with the high cost of obtaining work permits, account for their protracted financial dependence. Access to health care for these individuals is restricted to UNRWA, international organizations and the private sector, with the latter demanding high fees for its services. Uniquely in this field, UNRWA has made agreements with Palestinian Red Crescent Society hospitals in order to guarantee equity for Palestine refugees in access to secondary health care. In all other fields, a reimbursement scheme is in place for secondary and tertiary care.

Jordan hosts nearly 2 million Palestine refugees, most of whom have been granted citizenship based on criteria such as their place of origin and year of arrival in the country. Whilst they remain a potentially fragile sector of the population, Palestine refugees have been allowed to enter the labour market, can access the country's health services, and enjoy considerable social mobility. Those who emigrated from the Gaza Strip during or after the 1967 conflict, however, face restrictions on their access to higher education and jobs. They are therefore the most vulnerable group. In **Syria**, almost 500,000 Palestine refugees have full access to government services, including health care, to the labour market and have almost the same legal protection as Syrian citizens although they are not granted citizenship.

Almost 2 million Palestine refugees reside in the **West Bank** and the **Gaza Strip**. This population in particular suffers from the long-term effects of socio-economic hardship. This is due in large part to the current closure regime which effectively restricts the movement of people and goods in and around the areas. The fragmentation of the West Bank through settlements and military installations is generating disparity in public access to healthcare (Giacaman *et al*., 2009), making access to these services in East Jerusalem from other parts of the West Bank increasingly difficult for Palestine refugees. In the Gaza Strip, a blockade continues to impair critically the supply of essential medical goods, delaying reconstruction and hindering patient referral.

The population living in the oPt is having difficulty facing the long term effects of socio-economic hardship and the recent crisis the Gaza Strip has only aggravated its isolation and infrastructural decline. The combination of expanding settlements and outposts, limitations to movement of people and goods

due to the Barrier and a complex system of physical obstacles and checkpoints is progressively narrowing the possibilities that Palestinian residents of the West Bank have of accessing all services, including health care. As of 2007, more than 38% of the West Bank consisted of settlements, outposts, military bases and closed military areas. Nearly three quarters of the projected Barrier rout runs inside the West Bank and will isolate, once completed, approximately 10% of West Bank territory, including East Jerusalem that will be physically connected to Israel. There is a comprehensive system of 85 manned checkpoints and more than 460 physical obstacles regulating or preventing Palestinian vehicles from using roads primarily reserved for Israeli use. This implies long detours and waiting time and is leading to the formation of Palestinian enclaves within the West Bank. These are geographically separated one from the other by some form of Israeli infrastructure (settlements, outposts, military areas, nature reserves and the Barrier) where the road system functions as an adjustable corridor effectively limiting Palestinian movement as monitored by OCHA, 2008.

The socio-economic situation in the oPt is deteriorating rapidly. A sharp economic regression had already been documented in 2006, with a per capita GDP drop of 30% compared with 1999 in the oPts. The situation is particularly severe in the Gaza Strip where nearly 80% of the population was already living in conditions of extreme poverty by that time and the trend is pejorative. Consumption poverty rates per household have increased from 26% to 49% between 1998 and 2008, unemployment rates have reached 49% and more than half the population in the Gaza Strip was found to be food insecure (IRIN, 2007).

CONCLUSION

As an Agency working in a chronically unstable environment, UNRWA is continuously challenged to face crisis. Conflicts in Lebanon and more recently in the Gaza Strip have forced the health programme to react rapidly in order to ensure continuity of comprehensive primary health care delivery and to respond to new needs of refugees. It has led to the establishment of new services such as mental health, physiotherapy and rehabilitation to assist those affected by permanent disability. It has also made the Health Programme strongly decentralized and able to adapt rapidly to limits imposed by logistic impediments and security concerns. This has limited the disruption of services like epidemiological surveillance and treatment of chronic diseases that suffer the most in times of conflict. The result of these management choices has been a limitation of the consequences of socio-economic hardship and conflict on the health of Palestine refugees. Although UNRWA beneficiaries remain an extremely vulnerable population, MDG, demographic indicators and epidemiological trends are still in line with those observed in the region. Exception to this, are the worrisome signs arising from the Gaza Strip suggesting the need to specifically empower UNRWA health delivery in this location.

Logistic and security impediments coupled with the raising costs of drugs and human resources have raised the costs of delivering health to Palestine refugees. Confronted with financial impediments UNRWA is struggling to make ends meet. Sustained support from donors is essential if the efforts made by UNRWA to preserve refugees from the worst effects of socio-economic hardship in the past 60 years are not to be made vane by lack of human and material resources.

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Health research: the challenges related to ethical review and informed consent in developing countries

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Summary - The globalization of clinical trials, as well as the creation of funding mechanisms for research addressing the health problems of developing countries, have led to a significant increase in the number of research projects in the South. This paper reports on a workshop held by the *Switching the Pole Network* in Antwerp in December 2008 to assess the challenges of ethical review and of the informed consent process in vulnerable populations. A systematic approach to ethical review is needed, promoting trust among research partners and improving the efficiency of international ethical review practices, while building communication strategies across traditional geographical boundaries and power structures. At the moment, the double ethical review of research sponsored or funded by Northern organizations in resource-poor settings can minimize the risk of double standard practices and enhance the protection of study participants and populations. We also need guidance to prevent the exploitation of vulnerable populations in health research; in particular those whose participation is not based on a free choice but on the necessity to access otherwise inaccessible medical care or other benefits. We hope that the issues raised can feed a debate leading to better guiding principles on health research in resource constrained settings.

Key words: research ethics, developing countries, ethical review, informed consent

INTRODUCTION

Research addressing the health problems of developing countries is of paramount importance to individual and global health. The globalization of clinical trials, mentioned by Rehnquist (2001) and by the European Group on Ethics in Science and New Technologies (2003), as well as the creation of mechanisms and partnerships aimed at funding public health oriented medical research, have led to a significant increase in the number of research programs carried out in the South, often with the participation of Northern organizations. However, as showed by the WHO (2008), Schipper and Weyzig (2008), WEMOS (2008), Lancet Editors (2007) and Lenzer (2008), carrying out health research in resource-poor settings entails potential abuse and exploitation, among other factors because of the vulnerability of the research subjects and due to the weakness of the regulatory framework in which the research takes place (Glickman *et al*., 2009).

The *Switching the Poles Network* brings together researchers from Belgium, Burkina Faso, Cambodia, Cuba, Democratic Republic of Congo, Indonesia, Nepal, Peru, Uganda and Zambia, with the objective of jointly building the capacity to conduct medical research that addresses the needs of vulnerable populations according to sound ethical principles and standards as described in applicable guidelines, including the Nuremberg code (1947), the Helsinki Declaration (World Medical Association, 2008), the Belmont Report (US National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979), the Good Clinical Practices (World Health Organization, 1995;

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Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

International Conference of Harmonization, 1996) and the CIOMS Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2002).
During a workshop held in Antwerp, Belgium, in December 2008, the members of the Network discussed the challenges linked to the ethical review of medical research carried out in developing countries by Northern organizations, and those related to the informed consent process in vulnerable populations. The results of the workshop were presented at the 6th European Congress of Tropical Medicine (Verona, 2009), and further developed in a meeting hosted by the Forum of the European & Developing Countries Clinical Trials Partnership (Arusha, 2009).

THE ETHICAL REVIEW

The role of ethical review

Ethical review has seen considerable changes over time. Originally, the Ethics Committees (ECs) had a consultative role. However, article 15 of the current version of the Helsinki Declaration stipulates that research protocols "must be submitted for consideration, comment, guidance and approval" to the EC before the study begins. As such, the Declaration has shifted the ethical review process from being a private consultation process between researcher and institution to an essential research requirement and a factor of accountability to the public. It is the role of Governments to establish the legislative framework dictating the shared modality and rules for the ethical review of each independent EC (Crawley, 1997; TDR, 2000).

The double ethical review

"Double ethical review" refers to the procedure, applicable to North-South collaborative research, of submitting a protocol for ethical clearance in the country where the research will take place and in the country of the sponsor or funding organization. Although recommended by various authors (Bompart *et al*., 2008) and laid down in several guidelines [Nuffield Council on Bioethics (2002), European Group on Ethics in Science and New Technologies (2003), US National Bioethics Advisory Commission (2001)], to date no laws or regulations exist enforcing double ethical review. In some other instances, it has not even been substantially considered, or it has been seen as a paternalistic requirement. Within the *Switching the Poles Network*, all research protocols are subject to double ethical review, being sequentially submitted to the ITM Institutional Review Board (IRB), to the legally accredited EC of the Antwerp University Teaching Hospital (UZA) and to the competent EC in the country where the research takes place. Each protocol is examined from different perspectives.

A) The IRB of ITM and the EC of UZA

Though not legally accredited as an EC under the 2004 Belgian Law Concerning Experiments on the Human Person, the IRB of ITM provides an internal, preliminary review of all ITM-related research protocols, due to its specific expertise in tropical diseases and developing countries. In addition, it is expected to stimulate and maintain institutional expertise in research ethics and methodology.
The EC of UZA is accredited to carry out ethical review according to the Belgian Law. However, there are no specific qualification requirements for Belgian ECs that evaluate research carried out overseas.

B) The ethical review in the host countries: the example of the Democratic Republic of Congo (DRC) and Peru

Peru and the DRC represent two examples of challenges related to ethical review in developing countries.
In Peru, the number of commercial and non-commercial clinical trials has considerably increased between 1995 and 2008. Nevertheless, the number of non-commercial studies remains low as compared to industry-sponsored research. The number of ECs, located both in Lima and in the provinces, has expanded quickly which will sooner or later necessitate a review of the existing ECs for accreditation purposes. The main challenge for ECs here, as is the case for other emerging countries, is carrying out quality evaluations despite the high workload and providing public assurance that only research pertinent to the study population is carried out.
In the Democratic Republic of Congo (DRC), on the contrary, there are few research projects, they are mainly coordinated by foreign institutions, and ethical review is far from being routinely implemented (Maketa *et al*., 2009). There are only two fully functional ECs: the EC of the Public Health School in Kinshasa and the thematic EC of the National Program for the Treatment of Human African Trypanosomiasis. This scarcity of ECs and the geographical inaccessibility of many provinces represent major difficulties for ethical review, further aggravated by the lack of national legislation on health research and by the weakness of Drug Regulatory Authorities. In a country where, as a result of various humanitarian crises, the ethical review system is weak (Schopper *et al*., 2009), the main challenge is building and strengthening it.
Despite the differences, some problems are common to Belgium, Peru and DRC: for instance, the fact that many researchers still perceive ethical review as a burdensome obstacle rather than a fundamental step to protect individuals and populations, and the fact that the follow-up of the research by the EC after the initial approval is often insufficient.

The Network's recommendations on double ethical review

When Northern organizations conduct, support or sponsor collaborative research in the South, the double ethical review can contribute to ensuring the appropriate supervision of the Northern partner while limiting the consequences of the weakness of ECs in the host country's (Hyder *et al*., 2004; Hyder *et al*., 2009; Kass *et al*., 2007). The Network's members agreed that all medical research funded, sponsored, implemented or supervised by Northern organizations in developing countries should undergo a double ethical review, for three principal reasons:

- *Equity*. Given the North-South inequalities, the double review can help to avoid double-standard practices and prevent that exploitative studies are carried out by Northern organizations in the South;
- *Complementarity*. The complementarity of perspectives of Northern and Southern ECs can enhance the quality of the research and improve the protection of research subjects and populations;
- *Networking*. The double review process, if accompanied by proactive communication among ECs, can help to build trust and mutual learning. It was therefore suggested that protocols be submitted to Northern and Southern ECs simultaneously rather than sequentially: if comments are issued from one or more ECs, a single letter of reply would be sent to all ECs, making them aware of all the comments.

Further reflection is needed to establish rules dealing with disagreement: the respect of national sovereignty should be balanced with the need to ensure the strictest enforcement of ethical principles. The double ethical review should never lead to a decrease in the perceived responsibility of individual ECs: on the contrary, as indicated in 2008 during the Global Ministerial Forum on Research for Health (2008), there is a great need to work to increase the ownership of research in developing countries.

THE INFORMED CONSENT IN VULNERABLE POPULATIONS

Informed consent in health research

The requirement that individuals give voluntary consent to participate in medical research is based on the principle of respect, which originates from the belief that everybody has the right and the capacity to act voluntarily and with self-determination. Through the informed consent process, a person or his/her representative voluntarily agrees to participate in research, under the conditions of being informed of all the aspects relevant to the decision and maintaining a relationship of trust and communication with the researchers during the entire research.

The quality of the informed consent process and related ethical implications (Flory *et al*., 2004), is susceptible to several factors, including the individual characteristics of the researcher (personality, language skills, knowledge and perceptiveness to the local context, cultural and social sensibility, etc.) and of the participant (education and reading level, comprehension capacity, socio-cultural values and constraints, socio-economic status, etc.). Although most guidelines pay special attention to individuals whose free decision-making capacity is diminished or impaired because of legal or medical reasons (e.g., children, mentally disabled people, elderly, subjects in emergency situations or with incurable diseases, etc), there is a consensus in the bioethics literature that not only individuals, but also populations may have diminished autonomy and can be potentially vulnerable to exploitation: for instance, marginalized communities (Nakkash *et al*., 2009), people in hierarchical social structures, illiterate people, etc. This situation is quite frequent in resource-poor and rural contexts (Fitzgerald *et al*., 2002; TDR, 2007), due to socio-cultural and socio-economic factors, including language barriers, gender, peer and community pressure, dearth of health care and medicine, direct poverty and overall social vulnerability.

Free decision-making in particular may be impaired by the lack of access to adequate health-care. Most people in communities burdened with high disease rates and insufficient or inaccessible medical care cannot refuse to get the free, quality health-care services that are provided within the medical research projects and that are otherwise unavailable. In these populations and settings, therapeutic misconception is often greater, e.g. people expressing their gratitude to the research team for the "assistance" while being largely unaware of the research content.

Certain groups present more specific challenges: for instance, the Guidelines of the Uganda National Council for Sciences and Technology (web site) entitle minor mothers to give consent for the participation of their children in research projects. This choice is based on a delicate balance among social, cultural and legal factors, and on the notion of "adulthood" based on elements other than age, such as the person's social status.

The informed consent in health related social science research

Qualitative social science research and ethnographic studies in international health are guided by the same moral and legal principles of informed consent as health research and therefore require that partici-

pants are well and truthfully informed. The different nature of the research, the diverse characteristics of the participants and the different level of risk for respondents, however, may require a different application of the consent procedure, as described by the American Anthropological Association (2004). In ethnographic studies, the investigator uncovers the local social setting and cultural context by observing and by interacting both formally and informally with respondents in the field, making flexibility and informality key elements of research of this nature. Therefore, procedural requirements of written consent may in some cases create distrust between the researcher and respondent or lead to decreased reliability of results due to enhanced response bias.

The independent ECs are required to ensure the appropriateness of the informed consent process in social science research and any kind of health and non-health research carried out with human subjects, always taking into due account the vulnerability of the study population. Since ECs generally focus on health research, it is advisable that they get additional and specific expertise to evaluate research in borderline and non-medical fields - such as ethnographic studies.

On a different level, the social sciences can contribute to improving the quality of the informed consent procedure in medical research by providing tools to enhance the quality of the communication between the researcher and the participant and his/her community. In particular, social scientists can provide in-depth and contextualised information on how to construct context- and cultural-sensitive communication strategies with potential participants, reducing common cultural pitfalls and misunderstandings that often lead to low participation or increased drop-out rates and can seriously jeopardise health research ethics.

The Network's recommendations on informed consent process

- Individual informed consent is essential, irrespectively of the field of the research and of the characteristics of the population. Waivers granted by a competent EC should only concern the signature, never the process, and they should never be justified by the fact that the study population is poor or illiterate.
- Guidance is needed to prevent exploitation of vulnerable individuals and populations with diminished decision-making power concerning their participation in health research (including those lacking access to quality health care).
- Research institutions should try to reconcile the research of new therapeutic tools with the ethical requirement of making them accessible to everyone through quality health care systems. Even if achieving universal access to quality health care is a complex and long-term task, research institutions and sponsors could contribute to improving the quality of health care in their respective research settings on a project by project basis.
- The understanding of and sensibility for local socio-cultural values, constraints and contextual factors, always within the framework of universal ethical principles, is a prerequisite for respectful and ethical interactions between researchers and study participants in vulnerable contexts. Social scientists and anthropologists can help to design the research and consent tools accordingly, contributing to overall effectiveness, relevance and research ethics.

ACKNOWLEDGEMENT

The Switching the Poles Network is funded by the Belgian Development Cooperation.

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Screening for tuberculosis among asylum seekers: experience from an immigration centre in Central Italy and literature review

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Summary - Understanding the epidemiology of tuberculosis in migrant communities and designing adequate and comprehensive control strategies is a major challenge facing public health authorities in many low-prevalence countries. Asylum seekers are a particularly vulnerable subgroup of people who are required to live in hosting centres for several months waiting for their residence permit. Since September 2008, tuberculosis (TB) screening has been offered to all asylum seekers living in the hosting centre of Castelnuovo di Porto in Rome (C.A.R.A). This paper describes the results of this screening activity that aims to detect all asylum-seekers with active and latent TB infection, and provides an overview of the literature concerning TB screening among foreign-born people in low prevalence EU countries.

Key words: Tuberculosis, Asylum Seekers, Italy, Screening

INTRODUCTION

The epidemiology of tuberculosis (TB) in low prevalence EU countries has been changing in the last decades with foreign-born people experiencing a disproportionate burden of disease (Rieder *et al*., 1994; Raviglione *et al*., 1993; Johnsen *et al*., 2005; Ponticiello *et al*., 2005) compared with the general population. Imported tuberculosis has been identified as the cause of increasing notification rates for this disease in Italy and the UK between 1999 and 2003, notwithstanding the general decrease observed in the EU since the 1990s (Falzon and Aït-Belghiti, 2007). There is evidence to suggest that the risk of progression from latent TB to active TB infection is greatest in immigrants in the first 3-5 years after arrival in their adoptive countries (Talbot *et al*., 2000). This risk, compared to native population of TB low-prevalence countries, can persist also for decades following entry (Zuber *et al*., 1997). Among immigrants, refugees and asylum-seekers are at higher risk of having active TB upon arrival or of developing the disease in the host country (Bwire *et al*., 2000; Bonvin, Zellweger, 1992; Barr and Menzies, 1994; Van den Brande *et al*., 1997). A combination of high TB prevalence in the country of origin, difficult travelling and living conditions prior to arrival, poor living standards after arrival and lack of access to health care in the host country are among the main determinants of this phenomenon.

Although the foreign-born population accounts for a large proportion of reported cases of active TB in Europe [66.8% in Germany in 1994 (Rieder *et al*., 1994), 57% in the Netherlands in 1997 (Bwire *et al*., 2000), 44% in Italy in 2005 (Ministero della Salute, 2007), 48% in France in 2005 (InVS, 2007)] and this could result in an increased transmission within foreign-born communities (Dasgupta and Menzies, 2005), the public health impact on the general population has been proved to be low due mainly to two factors.

Firstly studies on the dynamics of TB transmission among foreign and native communities within low prevalence countries (restriction fragment length polymorphism studies) demonstrated that the estimated cases of active TB among native-born individuals that can be attributed to transmission from a foreign-born person is very low (2%-17%) (Dasgupta and Menzies 2005; Dhale *et al*., 2003). Secondly, notwithstanding the higher TB incidence among foreigners, absolute incidence and transmission rates are low, with prevalence among migrants estimated to be less than 1% in studies conducted in

Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

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Europe, the US and Canada (Dasgupta and Menzies, 2005).

Generalizations should however be taken with caution, particularly with diseases such as TB that are strongly influenced by the social determinants of health (World Health Organization, 2003). The level of social integration among different groups of immigrants in different environments is diverse and could change the likelihood of disease transmission within the host country community. A recent genotyping analysis among immigrants in Italy (Franzetti *et al*., 2009) showed that the proportion of TB isolates in clusters of immigrants and native patients was similar and that living conditions exert a more profound impact than ethnic origin on the likelihood of acquiring the disease.

Policies among EU Member States concerning the screening for tuberculosis are diverse (Easac, 2007), ranging from an absence of a national policy, as is the case in Italy, to different combinations of active and passive case finding (Bwire *et al*., 2000). Often evidence supporting the effectiveness of these different approaches is lacking (Coker *et al*., 2006) leading to difficulties in identifying models of best practice (Hargreaves *et al*., 2009). Moreover the choice of a cost-efficient screening strategy for TB in the EU is hindered by the low prevalence of the disease itself that leads to greater proportions of false positive test results and healthy people requiring costly follow-up diagnostic protocols.

Asylum seekers in the C.A.R.A. hosting centre of Rome, live in a relatively cramped environment (4-6 guests per room) having arrived to Italy after one or two years of travel in very harsh conditions. The vast majority come from sub-Saharan Africa. In 2008 Ethiopia, Somalia and Eritrea were among the most common countries of origin, however in the following months the origin of guests became more heterogeneous including many citizens of Nigeria, Ghana, Burkina Faso, Gambia and the Ivory Coast. The majority of these migrants are male, young with limited schooling and very low health literacy.

PATIENTS AND METHODS

During the period August 2008 - July 2009, 2058 asylum seekers have been hosted in the centre of Castelnuovo di Porto in Rome (C.A.R.A) for a time variable between two days and nine months (mean permanence 115 days). Around 300 asylum seekers per month attended the C.A.R.A. Health Centre for medical consultations. TB screening was offered to all asylum seekers who attended the Health Centre.

For each migrant who accepted the screening, the Centre's resident physicians conducted a screening interview and opened an individual file that contained all relevant demographic and clinical data. The screening tests used were the tuberculin skin test (TST), followed by chest-X ray and microbiological exams (smear examination) that were proposed if TB was clinically suspected based on initial findings or if the patient was symptomatic for pulmonary disease Figure 1. If a sputum smear exam was found positive for acid-fast bacilli (AFB) a BK culture was performed on the sample to confirm the aetiology. The TST was administered by sub-cutaneous injection of 5 IU. As the study population was mostly of sub-Saharan African origin, and therefore with a higher probability of previous exposure to Koch bacilli (BK) and/or bacillus Calmette-Guérin vaccination, TST was considered positive only if the area of erythematic infiltration around inoculation was ≥ 10 mm. Previous BCG immunization was enquired upon during the interview and vaccination scars looked for and documented. French and English-speaking migrants conducted the interview directly with the Centre's physicians while an interpreter assisted asylum-seekers speaking other languages. All patients who accepted to undergo TB screening were duly informed of all the procedures involved and signed a specific informed consent in a language that each could understand.

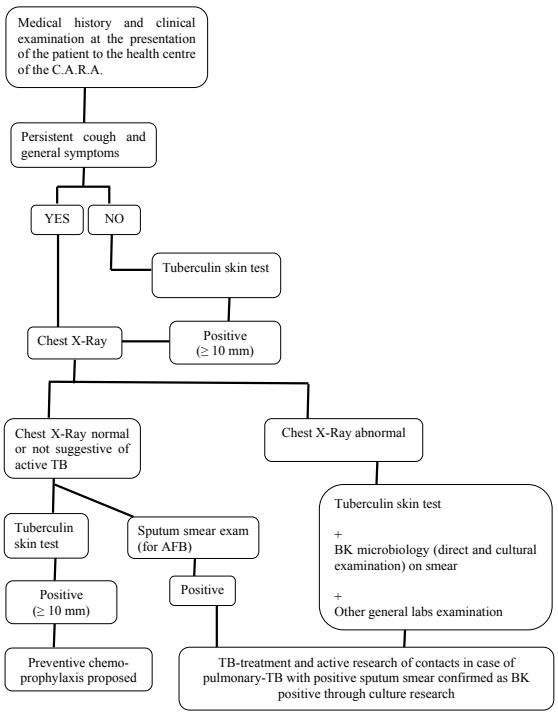


Figure 1 - Methodological algorithm of TB screening in the C.A.R.A. health centre.

RESULTS

235 people (86% male, median age 26 years) accepted to be screened for TB. No significant difference in the demographic profile compared with the general population of asylum seekers residing in

the C.A.R.A. centre at the time (Tabs. 1 and 2) was observed. 186 (79.1%) were asymptomatic for pulmonary disease and 49 (20.9%) complained of persistent cough and malaise. Almost all (92%) came from African Countries: 23% from Gambia, 19% from Eritrea, 13% from Somalia and 12% from Burkina Faso (Tab. 2).

Table 1 - Demographic characteristics of the general population of migrants hosted in the C.A.R.A. during August 2008 - July 2009 (*n*=2058).

		N	%
Sex	M	1791	87
	F	267	13
Age	0-18 years	55	2,6
	19-45 years	1989	96,7
	≥ 46 years	14	0,7
Region of origin	Horn of Africa	1002	48,7
	West Africa	289	14
	East Africa	571	27,7
	Maghreb	45	2,2
	Middle East	24	1,2
	East Asia	109	5,3
	Other	18	0,9

Table 2 - Demographic characteristics of migrants hosted in the C.A.R.A. screened for TB during August 2008 – July 2009 (*n* = 235).

		N	%
Sex	M	202	86
	F	33	14
Age	0-18 years	5	2,1
	19-45 years	229	97,4
	≥ 46 years	1	0,4
Region of origin	Horn of Africa	81	34,5
	West Africa	55	23,4
	East Africa	80	34
	Maghreb	1	0,4
	Middle East	3	1,3
	East Asia	8	3,4
	Other	7	3

All 49 symptomatic patients (Fig. 2) accepted to undergo a chest-X ray (CXR) and microbiological testing. In 8 cases, CXR was suggestive for TB and the TST was positive. Sputum was positive for tubercular bacilli only in one case. All these patients started a complete cycle of anti-TB therapy and contacts of the contagious patient were traced and offered TB-prophylaxis to reduce the risk of spreading the infection in the community. All 41 patients with negative CXR, had AFB-negative sputum smear exams. Only 30 of those accepted the TST. Among those, 21 had a positive result and were offered TB-prophylaxis for latent TB infection.

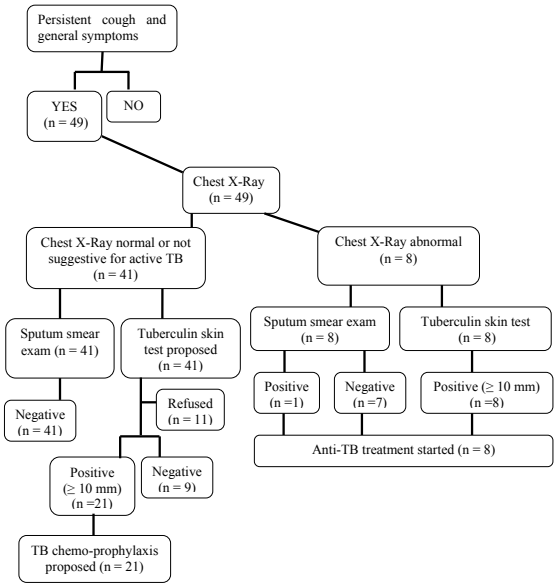
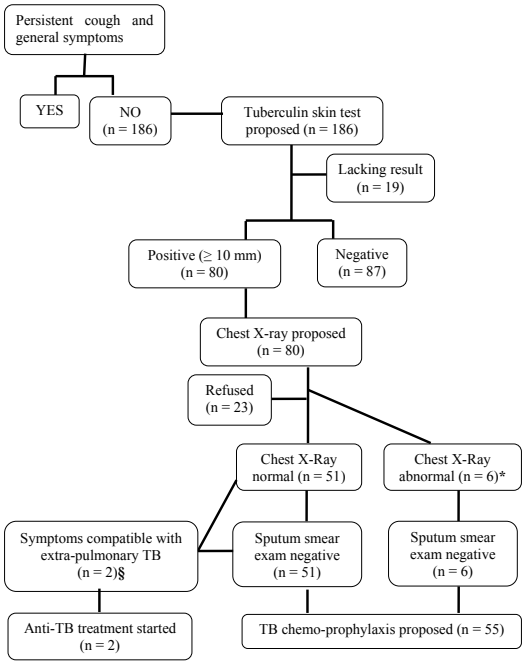


Figure 2 - Results of TB screening on symptomatic migrants hosted in the C.A.R.A. (n = 49).

Asymptomatic subjects (n=186) were screened with TST (Fig. 3). Although all accepted to perform the test, 19 out 186 (10.2%) didn't come back after 48h to collect the result. Among the 167 subjects who received a test result, 80 were found positive. A chest X-ray was offered to TST-positive patients, but 23 out 80 (28.7%) refused and were lost to



*radiological signs compatible with past pleuritis (n = 2) and past TB infection (n = 4)
§Scrofula (n = 1) and Pott's disease (n = 1)

Figure 3 - Results of TB screening on asymptomatic migrants hosted in the C.A.R.A. (n = 186).

follow-up. 57 patients underwent a CXR and a sputum smear exam. Six of those (10.6%) had an abnormal CXR. All 57 had AFB-negative sputum smear exams. A preventive TB-prophylaxis was proposed to all TST-positive patients except two who developed symptoms of extra-pulmonary TB during the screening period. One was diagnosed with scrofula (tubercular lymphadenitis of the neck) and one with Pott's disease (tuberculous arthritis of the intervertebral joints). These two patients started an appropriate anti-TB treatment. The 6 TST-positive patients with abnormal CXR showed radiological signs compatible with past pleuritis (n=2) and past TB infection (n=4).

10 cases of active TB were identified (detection rate 4.2%). 8 of those were diagnosed as pulmonary TB (one case was sputum positive) and 2 were affected by extra-pulmonary TB (one case of Pott's disease and one of scrofula). None had anamnestic or clinical findings suggestive of previous BCG vaccination.

101 cases of latent TB infection were identified (of which 80 among asymptomatic asylum seekers) with a detection rate of 43%. 23 of those patients were lost on follow-up, all others were offered prophylactic treatment.

The acceptation rate of TST among symptomatic patients was 77.6% (100% among those with abnormal CXR), while among asymptomatic patients it was 89.8%. CXR was accepted by all symptomatic patients while acceptance rate was 71.2% among TST-positive asymptomatic patients. Although 78 asylum seekers were considered eligible for pharmacological TB-prophylaxis, none of them accepted it.

DISCUSSION

Migration in the EU is a complex phenomenon driven not only by poverty and the desire for a better life (economic migrants) but also by more complex socio-political issues that compel internally displaced people and asylum seekers to seek safety outside their native environment. Today this specific group of migrants constitute a significant proportion of mobile populations (ECDC, 2009).

Scientific evidence suggests that people categorised as foreign-born have a higher burden of active TB in EU low prevalence countries compared with native-born people, and that the former tend to develop the disease at a younger age with higher treatment default rates and poorer outcomes (ECDC, 2009). In a review by Dasgupta, however, the absolute prevalence of active TB among migrants both considering studies conducted among economic migrants and asylum seekers in the US, Canada and the UK was always less than 1%, with higher rates of latent TB infection (latent TB with normal CXR ranged between 36% and 42%). A pattern also confirmed in a more recent article (Harstad, 2009). The diverse methodologies and populations on which these studies were conducted, should lead to caution when comparing data, however it is not surprising that the C.A.R.A. population screened in 2008, had a higher detection rate for this disease with a 4.2% prevalence of active TB (Tab. 3) while rates of latent TB infection were comparable. Most asylum seekers in the Italian C.A.R.A. come from countries endemic for TB and, as their travel is not economically motivated, they are not pre-selected among the youngest and healthiest of their communities as is the case of

Table 3 - Prevalence of Tuberculosis (TB) among migrants in low incidence countries, review by K. Dasgupta (2005[i]) and the C.A.R.A. population (2008)*.

Authors	Year	Population	Prevalence (%)			
			Active TB	Latent TB Infection		
				With CXR abnormalities	Without CXR abnormalities	Unknown CXR
Blum *et al*.	1993	Amnesty programme adjustments for illegal migrants from Mexico to the USA	0.08	5	42	NA
Markey *et al*.	1986	Port of entry screeninf of all immigrants to the UK	0.04	0.1	NA	NA
Pitchenik *et al*.	1982	Haitian refugees in the USA	0.65	NA	NA	NA
Nolan *et al*.	1987	SE-Asian refugees in the USA	0.8	5.6	35.7	NA
Dasgupta *et al*.	2000	Permanent resident applicants in Canada	0.15	2.6	NA	NA
Pacifici *et al*.	2008	Asylum seekers in central Italy	4.2 (10/235)	2.6 (6/235)	30.6 (72/235)	9.8 (23/235)

*Due to the different methodologies adopted in the different studies and the diverse populations, the comparison of this data serves only to gain a general, descriptive understanding of current knowledge of TB prevalence in different migrant communities in low prevalence countries. No further conclusions can be inferred.

[i]Dasgupta K., Menzies D. (2005). Cost-effectiveness of tuberculosis control strategies among immigrants and refugees. *European Respiratory Journal,* **25**: 1107-16.

the majority of job-seeking immigrants. Moreover the harsh travelling and living conditions before arriving to the centre are factors that may contribute to favouring the progression of disease from latent to active TB.

However, although imported TB may appear as the main issue to tackle in controlling this disease in low prevalence countries, the situation is more complex. As stated by the ECDC in 2009, material deprivation appears to be a far more relevant determinant for developing TB than the country of origin and also the European Academy Science Advisory Group (EASAG) identified socio-economic hardship in the host country as a leading factor to the development TB among migrants (EASAC, 2007).

It is well known that TB burden follows a strong socio-economic gradient between countries, within countries, and within communities, with a strong association of social deprivation and poverty with TB risk (Lonnroth *et al*., 2009). Moreover a migrant's proximate risk factors for acquiring this disease in a low prevalence country, excluding the prevalence of the disease itself the country of origin, include environmental factors and host factors. For example high risks of infection have been documented among prison staff, inmates and certain health care workers, while environmental aspects such as crowding, air flow and humidity have been correlated with an increased risk of transmission. It is also well known that factors that impair the host's immune system such as HIV infection, malnutrition, tobacco smoke, alcohol abuse, silicosis, diabetes, malignancies, immunosuppressive treatment can increase the risk of developing the disease (Lonnroth *et al*., 2009). All these proximate risk factors can help public health officers to identify at risk groups for tuberculosis within the so called "foreign-born" people.

Even though TB is an example of "social disease", the strategies adopted worldwide for its control have focussed mostly on medical interventions aimed at diagnosing and treating as many cases as possible. Also screening strategies for TB among migrants to low prevalence countries have concentrated on the disease rather than its social and biological determinants and consequently most targets have been set based on geographic origin (e.g. foreign born) and administrative requests (e.g. permanent residence applications). Evidence (Lonnroth *et al*., 2009) suggests that even massively scaling up case detection and treatment of active TB infections, thus reducing transmission, it would be hard to reach a sustainable reduction in prevalence and incidence of disease without additional efforts to prevent progression from infection to disease. This would be particularly true in low prevalence countries where transmission rates are low and reactivation of latent infections causes a higher proportion of new TB cases.

The controversial public health relevance of imported TB as opposed to its social determinants in the host country is the reason why the screening migrants and specifically asylum seekers has been the object of debate in Europe (Paterson, 2003). Given the epidemiology of the disease and the patterns of transmission observed in the EU, the issue of TB control is essentially a question of respecting an individual's right to be diagnosed and treated for a curable infectious disease (ECDC, 2009). This is also true for migrants and strikingly relevant for vulnerable groups among them such as asylum seekers. The chronic nature of TB as well as the long term risk of reactivation of latent infections after arrival within the host country, poses the problem of continuity of access and entitlement (Singer, 2004) to health care and health education and raises the issue of reducing the exposure of vulnerable groups to the social, environmental and biological risk factors for TB.

No consensus has been reached concerning modality and utility of screening for infectious diseases in migrants (Hargreaves *et al*., 2009), although there is evidence supporting its utility specifically in the control of tuberculosis (Liu *et al*., 2009). The population of asylum seekers screened for TB in central Italy had a higher detection rate of active disease compared with other migrant communities screened in low prevalence countries. The small sample screened and the particularly difficult travelling and living conditions that asylum seekers are exposed to, makes it difficult to draw any conclusion from this observation except that in this specific group TB-screening using a traditional diagnostic approach (TST, CXR and sputum smear) was useful in the early identification and treatment of cases of active disease and in offering prophylactic treatment and health education to contacts of contagious cases to reduce the spread of the infection within the centre's community. The acceptability of TST and CXR were high, with the highest rates of acceptance for the first test proposed (TST for asympomatic asylum seekers and CXR for people with symptoms of lung disease). Conversely there was no acceptance of prophylactic treatment among those diagnosed with latent TB infection, this has been explained as prevalently due to poor understanding of the need for prophylactic treatment of disease. It is however a cause for concern given the public health relevance of prophylaxis in preventing TB progression, and has highlighted the need to strengthen health education, focussing on the various levels of disease prevention, during TB screening initiatives.

The C.A.R.A. centre integrates internal and external activities facilitated by the continued presence of

dedicated interpreters and cultural mediators and in collaboration with local authorities. In the centre migrants are offered shelter, food, primary health care, psycho-social support, health education and protection, while externally they are encouraged to participate to integration- facilitating activities such as schooling and professional training of adults.

From a public health perspective this study supports the hypothesis that in an asylum centre context, where the priority is the wellbeing of a small resident community, active screening and early treatment of disease as part of a more general "healthy life approach" can limit the spread of TB among its guests. However, more efforts are needed to increase acceptability of prophylactic treatment in order for it to be more efficient.

The challenge to provide an efficient TB control service after migrants leave hosting centres remains. This is particularly relevant for asylum seekers who, depending on the reasons of forced migration, may have weaker social ties with the country of origin and with their compatriots living in the same host country compared with economic migrants. The integration of all migrant related health care services, including those conducting communicable disease control activities, with the national public health service as has been suggested in the past in the UK (Paterson, 2003) seems to be the most rational approach to the problem. The urgency is not only to provide access to health care, but adequate health literacy to understand the proximate risk factors of TB and the need for medical follow up and preventive treatment in case a latent infection is confirmed. To do such things however the health of refugees and other migrants should be addressed comprehensively rather than disease specifically. There is a need for greater integration migrants within the host country's primary health care and social relief system, where socio-economically vulnerable groups can be identified and post-entry screening initiatives, planned according to efficiency and cost-effectiveness, implemented. This will have beneficial impact not only on the health of these individuals but also on the public perception of disease by helping to dislodge a common misconception in low prevalence countries that tuberculosis is more a disease of migration than of socio-economic hardship.

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Assessing the knowledge and behavior towards HIV/AIDS among youth in Northern Uganda: a cross-sectional survey

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Summary - Youth represents a vulnerable group to HIV and accounts for 45% of new infections globally. Attaining an accurate knowledge on HIV among young people is a vital objective of HIV prevention activities. In Uganda, 30% of young women and 35% of young men have comprehensive knowledge of HIV/AIDS. This is lower in the Northern region that was hit by a 20-year long rebellion and population displacement. The Northern Uganda Malaria AIDS/HIV and TB Program involves the youth with multifaceted preventive activities. A survey was conducted to assess their knowledge and attitude towards HIV. A total of 1,781 individuals were interviewed. Overall, 51% mentioned the three main ways of preventing HIV and 29% had a comprehensive knowledge on HIV transmission. Out of the respondents, 86% knew of a site providing HIV testing, 64% had ever tested for HIV and 76% knew of a condom distribution outlet. Factors like gender, geographical location, marital status and education were found to be associated to the above variables. Assessing the level of knowledge and the attitude towards HIV among the youth is vital for monitoring prevention programmes, identifying gaps and refining activities.

Key words: HIV/AIDS, youth, LQAS survey, Northern Uganda

INTRODUCTION

More than 25 years after the first case of AIDS was notified, the HIV pandemic continues to pose unprecedented challenges to individuals, families, health services and governments, especially in developing countries, which bear the greatest burden of HIV infection.

Young people are particularly affected in terms of transmission, vulnerability and impact. Globally, 45% of the new HIV infections occurred in 2007 was among the young people. Today, nearly 12 million young people are living with HIV/AIDS (UNAIDS, 2008). Particularly, HIV prevalence among young women is considerably higher than among young men in countries with generalized epidemics (WHO, 2003) and adolescent girls are especially vulnerable to HIV infection. Currently, about two thirds of newly infected adolescents aged 15-19 years in sub-Saharan Africa are female.

In 2007, national surveys across several African countries found that 40% of young males and 36% of young females had accurate knowledge regarding HIV, still well below the 95% goal for young people's HIV knowledge unanimously endorsed by Member States in the Declaration of Commitment on HIV/AIDS (UNGASS, 2008). Additionally, both in sub-Saharan Africa and globally, young women had lower levels of basic HIV knowledge than males.

Attention is turning increasingly towards young people, who are not yet sexually active or who are just embarking on their sexual lives. Promoting wider HIV-related knowledge and safer sexual behaviors have been some of the imperative areas of prevention for most national AIDS Control Programmes in those countries that are most affected by the epidemic (Ross *et al*., 2006).

Uganda is considered to be one of the world's earliest and most convincing success stories in combating the spread of HIV and reversing the trend of HIV epidemic. After reaching a peak of around 18% in 1992, the national HIV prevalence rapidly declined to 6% in 2000 due to a soundly funded and widely acclaimed policy approach and intervention strategy. However, this progress has been undermined by the recent statistics indicating that the HIV prevalence has been leveling off or even reversing.

The Uganda HIV Sero-Behavioural Survey (UHSBS) 2004/05 found an overall national HIV prevalence rate of 6.4% among men and women aged 15-49 years (Ministry of Health, 2006). The survey showed that prevalence was higher among

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Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

women (7.3%) compared to men (5.2%), and more so among the youth (3.9% among female vs. 1.3% among male). Additionally, 30% of young women and 35% of young men have comprehensive knowledge of HIV/AIDS(*). Knowledge increases with education and wealth and varies greatly by region. Of the 810,000 HIV-infected people estimated to live in Uganda in 2007 about 160,000 are youth (UNAIDS/WHO, 2008).

Study context and study objective

The North-Central region of Uganda was faced with a 20 year armed insurgency which resulted in immense suffering and the displacement of 1.8 million people, mostly from the four districts of the Acholi sub/region. The long term displacement has led to social deterioration, heavy dependency on food rations and a collapse of social services, including health services, with the exception of those provided to Internally Displaced People (IDP) camps residents by non-government organizations.

The UHSBS 2004/05 indicated that there is a high regional variation in HIV infection particularly in the conflict-affected North-central Region where the prevalence was 8%. This higher prevalence could be attributed to various factors, including the long-standing conflict with its displacement of populations, food insecurity and abject poverty leading to transactional sex, all of which compounded by lack of access to health care in the conflict-stricken areas. The same survey also revealed that the HIV comprehensive knowledge among the youth in this region is lower than the national average and the gap between male and female is much wider (32% among male vs. 17% among female).

The Northern Uganda Malaria, AIDS/HIV and TB Program (NUMAT) is a USAID/PEPFAR-funded project that begun in 2006 with the goal of expanding access to and utilization of HIV, TB and malaria prevention, treatment, care and support services in Northern Uganda. One of NUMAT's major target groups is the youth (15-24 years), particularly for prevention interventions. Through a multidisciplinary approach, NUMAT is using media campaigns, peer counseling, life skills training, and activities for youth in particularly vulnerable circumstances to spread prevention messages and help them develop the skills necessary to protect themselves. Among other key messages, the Program encourages delaying sex debut among young people; promoting lifelong, mutually monogamous partnerships; and reducing the number of sexual partners and making consistent use of condoms during casual intercourses.

A deep understanding of the knowledge of young people about HIV transmission and prevention as well as their attitude towards the epidemic is required to design and implement preventive interventions and monitor their effectiveness and appropriateness in providing the youth with the necessary information and protecting them from getting infected.

MATERIALS AND METHODS

Study population and study design

The Program employed the Lot Quality Assuring Sampling (LQAS) survey methodology to examine the HIV-related knowledge, attitude and practice among youth in Northern Uganda. LQAS approach is a relatively simple, low-cost sampling method (Lemeshow and Taber, 1991) that has widely been used in the health sector to determine the coverage of certain interventions (e.g. immunization) and to assess sexual behavior, risk factors and people attitudes towards HIV/AIDS (Robertson and Valadez, 2006).

The study population was the young people (age 15-24 years) residing in the nine districts of the Northern Region. Using the LQAS methodology, each district was divided into 5 supervision areas and for each supervision area 19 villages were randomly selected, where one eligible respondent was randomly identified and interviewed. Beside youth, the survey had targeted other categories of respondents, including male and female in their reproductive age and mothers who had a pregnancy in the two years prior to the survey. Some of these selected people turned out to be youth, thus increasing the total sample of 15-24 years old individuals to 1,781.

Data collection

Semi-structured survey questionnaires were developed investigating different areas. One in particular included specific questions on knowledge, attitude, practice and behavior of respondents towards HIV/AIDS. Interviewers with medical background and fluent with the local languages were identified and trained. The training consisted of an in-depth orientation to the LQAS methodology, including random sampling of villages and individuals, as well as interviewing techniques. The whole survey questionnaire was reviewed during the training, each question translated into the local languages and the final tool was eventually pre-tested.

Data collection took place between November and December 2008. Each individual interview began

*Comprehensive knowledge about HIV/AIDS combines knowledge on the three main ways of preventing HIV transmission (by abstaining from having sex; having sex with only one faithful, uninfected partner; and by using condoms) with rejection of the main misconceptions about HIV (knowing that a healthy-looking person can have the AIDS virus, and that HIV cannot be transmitted by mosquito bites or sharing food with a person who has HIV).

with an oral consenting process in which the interviewer explained the details of the study, including the participant's right to refuse to participate. In order to protect the confidentiality of all information provided, the data from this survey have been kept in a locked storage area with limited access. A unique identification number was assigned to each respondent and coded onto the survey questionnaire during data collection. No identifying information was included that would allow anyone to connect individual survey responses back to individual respondents.

Quality assurance and control of the data were integral components of the entire survey process at every stage, from instrument development to training of interviewer staff, to data entry, analysis and reporting.

Statistical analysis

The data entry process was made using EpiData v3.1 software (The EpiData Association, Odense Denmark). A programmed EpiData screen and logical checks for missing data were prepared. Proportions were computed to determine the status of each indicator and statistical tests (chi-square and odds ratio) were used to assess 95% level statistical significance. STATA statistical software was used to calculate the proportions and significance levels.

RESULTS

A total of 1,781 individuals aged 15-24 years from 855 villages throughout the region were interviewed. The socio-demographic characteristics of respondents are shown in Table 1. Female participants were predominant since some of the targeted respondent groups were obviously represented by women, namely the caretakers of children under 5 years of age and mothers who gave birth within two years prior to the study.

Knowledge of and attitude towards HIV among respondents are summarized by Table 2. More specifically, Table 3 shows that 72% indicated use of condoms as a way of preventing HIV infection, of which 80% knew where to locate a condom distributing outlet.

Concerning HIV testing, a substantial proportion of respondents (64%) reported to have been tested for HIV at any time and slightly more than half of them (51%) to have been tested and received the test result in the 12 months prior to the interview. The previous experience with HIV testing among participants is shown in Table 4.

Some factors were found to be associated to owning a comprehensive knowledge about HIV prevention.

Table 1 - Demographic characteristics of respondents

Variable	Number of respondents	Percentage
Sex		
Female	1,124	63%
Male	657	37%
Education		
No education	121	7%
Primary schooling	1,219	68%
Secondary +	431	24%
No answer	10	1%
Marital Status		
Single	646	36%
Currently in union	1,083	61%
Formerly in union	48	3%
No answer	4	-
Sub/region		
Lango	998	56%
Acholi	783	44%
Total	**1,781**	**100%**

Table 2 - Knowledge of and attitude towards HIV

Variable	Number of respondents	Percentage
Mentioned the three main ways of HIV prevention	910	51%
Rejected the common misconceptions on HIV transmission	882	50%
Had comprehensive knowledge of HIV prevention	517	29%
Mentioned the three ways of mother-to-child HIV transmission	867	49%
Keep secret if a family member had AIDS	726	41%
Willing to care for family member with AIDS	1,663	93%

Table 3 - Knowledge about condom use and availability

Variable	Number of respondents	Percentage
Mentioned condom use as a way of HIV prevention	1,282	72%
Knowledge of a condom distributing outlet	1,356	76%
Of those who mentioned condom use as a way to prevent HIV, knowledge of a condom distributing outlet	1,020	80%

Table 4 - Respondents' experience with HIV testing

Variable	Number of respondents	Percentage
Knowledge of HIV testing site	1,525	86%
Ever tested for HIV	1,131	64%
Of those who ever tested, willingness to disclose their sero-status	945	53%
Tested in the last 12 months	947	53%
Received the test result in the last 12 months	907	51%

Among them, male gender (p<0.001), educational level (p<0.001) and residing in the Acholi sub/region (p<0.001) were statistically significant.
Respondents from the Acholi sub/region were also more likely to have ever been tested for HIV compared with youth from the Lango sub/region (p<0.001). Similarly, female gender was also significantly associated with a higher proportion of people being tested (p<0.001), while education did not show any relation. Married and divorced people were more likely to have tested than those not in any marital relationship.
No association with these factors was found to exist for other indicators, namely: the willingness by respondents to disclose their sero-status once they tested; their intention to keep as a secret that a family member has HIV/AIDS and to care for a relative affected by the disease.
Statistically significant predictors of respondents' knowledge of where to locate a condom distributing site were male gender (p<0.001), education (p<0.001) and residing in the Acholi sub/region (p<0.001). The above findings are summarized in Table 5.

DISCUSSION

Assessing the knowledge, attitude and practice of the youth towards HIV/AIDS is vital to monitor preventive interventions and to measure progress in achieving set objectives, more so in countries largely hit by the HIV pandemic. Northern Uganda was found with HIV prevalence higher than the national average. It is debatable whether this is an effect of the long-standing conflict that affected the region, since there is no consensual evidence on this association (Spiegel 2004, Becker 2008). However, this highlights the strategic importance of expanding prevention efforts in this geographic area, including the provision of detailed and precise information about HIV infection, its modes of transmission and ways to prevent it. Young people are particularly vulnerable to HIV infection and they represent a crucial target group for preventive activities.
This study found that the comprehensive knowledge of HIV transmission among the youth in Northern Uganda in 2008 was at 29%, lower than the national average of 32% that was measured in the national survey in 2005 (Ministry of Health, 2006). Higher knowledge of HIV prevention was significantly

Table 5 - Odds ratios for assessed indicators

Variable	% with comprehensive knowledge	OR (95% CI)	% ever been tested for HIV	OR (95% CI)	% knowing where to obtain condoms	OR (95% CI)
Sex						
Female	23%	1.0	69%	1.0	71%	1.0
Male	30%	1.4 (1.2-1.8)*	54%	0.5 (0.4-0.6)*	85%	2.4 (1.8-3.1)*
Education						
No education	17%	1.0	69%	1.0	51%	1.0
Primary schooling	23%	1.5 (0.9-2.4)	61%	0.7 (0.5-1.0)	74%	2.7 (1.8-3.9)*
Secondary +	36%	2.8 (1.7-4.7)*	68%	0.9 (0.6-1.4)	90%	8.2 (5.1-13.1)*
Marital Status						
Single	30%	1.0	47%	1.0	76%	1.0
Currently in union	23%	0.7 (0.5-0.8)*	73%	3.0 (2.4-3.7)*	76%	1.0 (0.8-1.3)
Formerly in union	29%	0.9 (0.5-1.8)	71%	2.7 (1.4-5.1)*	73%	0.8 (0.4-1.6)
Ethnicity						
Lango	18%	1.0	53%	1.0	71%	1.0
Acholi	36%	2.5 (2.0-3.1)*	77%	3.0 (2.5-3.8)*	83%	1.9 (1.5-2.4)*

*p<0.001

associated with education status and sex, with male respondents rating better for this indicator. Lower literacy level of female respondents and limited access to HIV/AIDS educational messages could be reasons for these findings. Interestingly, a significant difference for this indicator was also found between the two sub-regions. The basic difference is that the population in the Acholi sub-region has stayed longer in IDP camps as a consequence of more intensified conflict and prolonged fighting in that area. This has resulted into a humanitarian emergency that attracted a large number of agencies and international NGOs for relief support and provision of health services to the IDP, including HIV-related services. This may suggest that the reason for the youth in the Acholi sub-region to have a better knowledge of HIV transmission than their age mates in the Lango sub-region could be the abundant exposure they received in terms of general HIV interventions and specifically preventive messages. Additionally, concentrated populations like those in congested IDP camps can be reached more easily by health-related activities than those living scattered in a rural context that is difficult to reach out.

This same geographic pattern was shown also in the uptake of HIV counseling and testing. A significant difference was found with Acholi respondents three times more likely to have ever tested for HIV than Lango respondents. More widespread availability and easier accessibility to testing facilities in that sub-region facilitated by the presence of several organization delivering HIV services is likely to be the main reason for the huge difference.

HIV testing among female participants was almost two-fold higher than their male counterparts, confirming a finding substantiated in both the 2004-05 UHSBS and the 2006 Demographic and Health Survey (UBOS, 2007). The female population seemed to have more opportunities to get tested for HIV. This may be due to their higher access to health facilities as patients and care-takers. Additionally, they are also likely to be counseled and tested during pregnancy in the context of the prevention of vertical HIV transmission. On the other hand, education did not appear to be associated to uptake of HIV testing. However, when gender was taken into account, there was an increased likelihood for HIV testing among educated males, which is not found among females for the reasons above.

This study did not investigate sexual behaviors or utilization of condoms during sexual intercourses. However, youth's awareness of consistent condom use as a way to prevent HIV transmission was examined and found to be high, especially among male respondents. Similarly, knowledge of a place where to access condoms was also found to be relatively high, with a significant association with gender and geographical region and a very strong one with education level. Education is a well known driving factor for better knowledge about condoms and condom use (ZELLNER, 2003). The difference between genders is likely to originate from social and cultural factors that privilege men in accessing condoms. Our study has also shown that there was a significant difference between the two geographical areas. This may be related to the similar difference noted for the indicator on the comprehensive knowledge of HIV transmission and explained with the intensified preventive efforts and wider availability of information spread across those districts hosting IDP camps by the several organizations that were involved in the humanitarian intervention.

This study has some limitations. Since respondents were asked to report on information from their past, such as uptake of HIV testing, it is possible that their responses did not accurately reflect their experiences because of recall bias. Response bias was also of concern as respondents might have intentionally reported on their own behavior or experiences incorrectly based on a perceived desirability of responses rather than actual knowledge or practices. Due to the cross-sectional design of the survey, it was only possible to speculate about associations between various factors and the resultant measures of each indicator, but any attribution of this outcome to specific interventions or programs might not be possible.

In conclusion, assessing the level of knowledge on HIV and the attitude and practice towards HIV services among the youth is a vital endeavor for monitoring the progress of HIV prevention programmes, identifying information gaps and factors related and refocusing the planning and implementation of preventive activities. Quick, simple and low-cost small scale surveys such as the LQAS can be utilized for measuring performance-related indicators, comparing with national and regional average and follow time trends. The quest for updated information on young people can be of enormous importance bearing in mind the many factors that increase young people's vulnerability to HIV during this critical period of their lives.

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Malaria surveillance in Italy: the 2000-2008 national pattern of imported cases

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Summary - The present study analyzes the trend of the imported malaria cases in Italy in the period 2000-2008, focusing on the changes in epidemiological features occurring in Italian and foreigners, in particular in settled-immigrants visiting relatives and friends (VRFs). According to other studies carried out in EU countries, this group is the most at risk of contracting malaria, being often unaware to have lost their transient immunity. Malaria cases recorded by the Ministry of Health and confirmed by the Istituto Superiore di Sanità were analyzed, using dedicated software. In the study period a constant decrease of the imported malaria cases was observed in both groups. In details, among Italians the reduction was 60%, while among foreigners was 33%. The mortality remains quite stable and always below the average of the other European countries. However, the risk of contracting malaria, in particular *P. falciparum* malaria (83% of the total cases) still remains very high in particular for people visiting African countries (93% of cases).

Key words: Imported malaria, Italy, Epidemiology, Malaria incidence, Travel medicine

BACKGROUND

Malaria still represents the commonest imported disease into Italy, as well as into the other European countries (WHO-CISID web site; Boccolini *et al*., 2007; Jelinek, 2008). In this last decade the Italian National Health Service (NHS) has increased its efforts to promote the awareness of travelers to malaria endemic countries about the risk of this infection, giving them up-to-date information on new effective prophylaxis drugs. In our country, since the eradication in the early 1950's, malaria is a mandatory reportable disease. The Ministry of Health (MoH) and the Istituto Superiore di Sanità (ISS), the Italian National Health Institute, are in charge of a surveillance system that provides diagnosis confirmation and a continuous outline of the epidemiological situation and, in case of necessity, an appropriate prevention and vector control intervention plan. In Italy, imported cases of malaria reached the peak of more than 1,000 in 1999 (Romi *et al*., 2001). Since then the total number of reported cases among both Italians and foreigners has been declining (Boccolini *et al*., 2007a). Nevertheless this disease still remains the main health threat for people travelling tropical and sub-tropical countries, in particular for settled-immigrants travellers, visiting relatives and friends (VRFs). The present study analyzes the trend of the imported cases in the period 2000-2008, with particular reference to the changes in epidemiological features occurring in Italian and settled-immigrant groups.

METHODS

The 2000-2008 malaria cases recorded by the MoH (Department for Health Prevention, Section Infectious Diseases and International Prophylaxis), from the Local Health Units of the NHS, and microscopically confirmed by the ISS (Malaria Unit, Department of Infectious, Parasitic and Immune-Mediated Diseases) were analyzed, using *ad hoc* software. Malaria cases have been classified by origin following the World Health Organization terminology (World Health Organization, 1963).

RESULTS

In the study period the number of reported malaria cases reached a total 6,377. Among these nine were autochthonous cases originated by accidental events as transfusion (N=1), transplantation (N=1), nosocomial (N=4) or baggage malaria (N=3) (Moro *et al*.,

Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

2002; Zamparo *et al*., 2005; Menichetti *et al*., 2006). 6,368 cases were imported, 1,749 (27.5%) occurred in Italian citizen and 4,619 (72.5%) in foreigners, more than 80% of which occurred in settled-immigrant group (Tab. 1). From 2000 to 2008, imported malaria cases dropped from 977 to 583 respectively, with a total reduction of about 40%. In details, among Italians the reduction was 60%, while among settled-immigrants was 33% (Fig. 1).

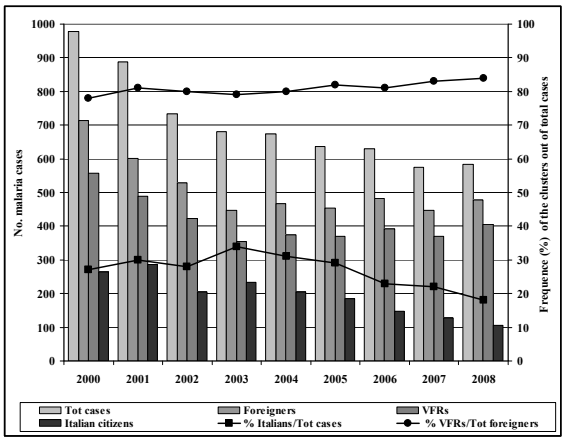

Figure 1 – Trend of imported malaria cases in Italy in 2000-2008. Dark grey columns represent settled-immigrants (VRFs) out of the foreigner cases (medium grey columns). The square black line shows the declining rate of Italians within the total cases; the round black line shows the rate of VFRs out of foreigner total number (right axe).

Most of the total cases were contracted in Africa (93%). In particular, as shown in previous studies (Romi *et al*., 2001a; Boccolini *et al*., 2007; 2007a), the majority of cases among foreigners (89.5%) originated from Western African countries, being Nigeria, Ghana, Ivory Coast, Burkina Faso, Senegal and Cameroun the countries mainly involved (Tab. 2). *Plasmodium falciparum* was the etiological agent in 83% of the total cases and 82% of these contracted in Africa, *P vivax*, responsible in average for 8.4% of the total infections reported, is predominant outside Africa, (76%, 87% and 85% in Asia, Central-South America and Papua New Guinea respectively). *P. ovale* was responsible of 6.5% of the total cases and *P. malariae* of about 1.6%, most of which (>95%) contracted in Africa for both species. Mixed infection were 22, 21 of which arose from Africa and one from Asia (*P.f.*+*P.v.*). Twenty-seven deaths, due to *P. falciparum*, occurred in the study period, corresponding to an annual average fatality rate of 0.5% (Tab. 1). A marked difference of fatality rate between the population group of Italians (about 1.6%) and foreigners (0.2%) was also recorded (Fig. 2).

DISCUSSION

In Italy in 2000-2008 a constant decrease of the imported malaria cases was observed, both in Italians and settled-immigrant groups. The mortality remains quite stable and always below the average

Table 2 – Imported malaria cases in Italy (2000-2008) in immigrants visited Africa. Cases are detailed by main visited West Africa (W.A.) countries.

Cases from Africa 4,411 (95.5%) Cases from West African Countries 3,946 (89.5%)	
Nigeria	1,047
Ghana	811
Senegal	800
Ivory Coast	499
B. Faso	327
Cameroun	228
Other W.A. Countries	234

Table 1 – General features of imported malaria in Italy 2000-2008. In brackets the relative frequencies (%) by nationality with respect to the total reported cases.

Features	Total cases	Italians	Foreigners
Malaria cases	6,377	1,756	4,621
Autochthonous	9	7	2
Imported	6,368	1,749 (27.5%)	4,619 (72.5%)
P. falciparum	5,301 (83.1%)	1,284 (73.1%)	4,017 (87.0%)
P. vivax	536 (8.4)	284 (16.2)	252 (5.5)
P. ovale	413 (6.5)	153 (8.7)	260 (5.6)
P. malariae	105 (1.6)	31 (1.8)	74 (1.6)
Mixed infections	22 (0.3)	4 (0.2)	18 (0.4)
*Africa	5,922 (93.0%)	1,511 (86.4%)	4,411 (95.5%)
Asia	296 (4.6)	142 (8.1)	154 (3.3)
C.S. America	123 (1.9)	71 (4.1)	52 (1.1)
Oceania (Pap.NG)	27 (0.4)	25 (1.4)	2 (0.04)
Deaths	27	20	7
P. f. fatality rate	0.51%	1.56%	0.20%

*autochthonous cases (N=9) not considered

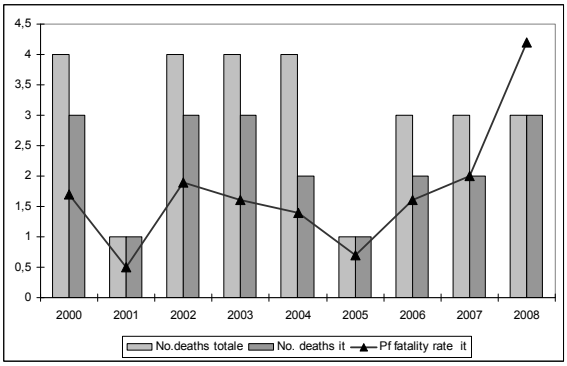

Figure 2 – Number of total deaths and deaths occurred in Italians in 2000-2008 (histograms). Line indicates *Plasmodium falciparum* fatality rate in Italian travellers (right axis).

of the other European countries (WHO-CISID web site; Jelinek, 2008). Nevertheless the risk of contracting malaria, in particular *P. falciparum* malaria, is very high for people visiting African countries. According to other studies carried out in EU countries (Schlagenhauf *et al*., 2003; Angell and Behrens, 2005; Askling *et al*., 2005), also in Italy, malaria continues to be a challenge in the population group of VRFs that are often unaware to have lost their transient immunity. In Italy the main source of settled-immigrants is represented by people from African "French speaking" countries, as already recorded in the previous decade (Romi *et al*., 2001a). The entity of this population is constantly rising up, representing only 15% of the imported malaria cases among non Italian citizens in the last decade of the 1900's (being predominant at time immigrants at the first entry in Italy) versus more than 75% in the study period (Boccolini *et al*., 2007a). Low use of prophylaxis in this population is of major concern for Italian Health Authorities especially in light of recent high rates of severe malaria (Jelinek, 2008). Primary care physicians play an important role in pre-travel advice to prevent the complications of malaria (Bisoffi *et al*., 2003; Lehky, 2005; Lalloo and Hill, 2008; Schlagenhauf and Petersen, 2008). Further efforts are needed to educate travelers, in particular settled-immigrants, about the need for prophylaxis and other protection measures when visiting tropical and sub-tropical countries endemic for malaria.

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Prevention of fecal-orally transmitted diseases in travellers with an oral vaccine

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Summary - *Background*: We analysed the data collected from questionnaires administered to air passengers at risk of travellers' diarrhea and cholera, most of whom had taken the oral anti-cholera vaccine Dukoral. *Materials and Methods:* Between 2008 and 2009, 182 questionnaires were collected at seven travel medicine clinics in Italy from 97 males, 84 females and one subjects of unspecified gender, with a mean age of 39.3 years. *Results*: Most of the trips were for tourism (78.6%), and the mean duration of the trips was 19.4 days. 87 of the travellers visited Africa, 61 Asia, 29 Central and Southern America, and 5 other Countries. Dukoral was taken by 123 subjects, and no serious adverse events were reported, with a good compliance. During the trips, 17 immunised subjects reported diarrhea (9 mild, 6 moderate and 2 severe cases); 5 subjects were prevented from carrying out their planned activities, 3 received medical care, but no one was hospitalised. *Discussion*: The incidence of diarrhea among vaccinated subjects was 13.8%, lower than the 17.4-23% reported in other recent studies and tolerability was more than satisfactory. In conclusion, the oral anti-cholera vaccine Dukoral could be an interesting proposal for the prevention of feco-oral diseases in travellers.

Riassunto - *Introduzione*: Sono stati analizzati i dati raccolti da questionari somministrati a passeggeri recatisi in aereo in zone a rischio per diarrea del viaggiatore e colera. La maggior parte dei passeggeri ha assunto il vaccino anti-colera orale Dukoral. *Materiali e metodi:* Nel periodo 2008-2009, sono stati raccolti 182 questionari presso sette Servizi di Medicina dei Viaggi (97 maschi, 84 femmine, 1 soggetto di sesso non riportato; età media 39,3 anni). *Risultati:* Il 78,6% dei viaggi aveva scopi turistici e la durata media è stata di 19,4 giorni. Un totale di 87 viaggiatori ha visitato l'Africa, 61 l'Asia, 29 il Centro-Sud America e 5 altri Paesi. La compliance verso il vaccino è stata buona: 123 soggetti l'hanno assunto senza riportare eventi avversi severi. Durante in viaggio, 17 soggetti vaccinati hanno avuto diarrea (9 casi lievi, 6 moderati, 2 severi). Cinque soggetti non sono riusciti a svolgere le attività programmate, 3 hanno ricevuto cure mediche, nessuno è stato ricoverato. *Discussione:* L'incidenza di diarrea tra i vaccinati è stata del 13,8%, minore di quella riportata in studi recenti (17,4-23%) e la tollerabilità è stata più che soddisfacente. In conclusione, il vaccino anti-colera orale Dukoral può ritenersi un'interessante proposta per la prevenzione delle patologie orofecali nel viaggiatore.

Key words: cholera, vaccination, travellers' diarrhea, questionnaire

INTRODUCTION

Over the last few decades, globalisation has led to an increase in international travel for holidays, work or humanitarian reasons, from mainly industrialised countries to countries with lower hygiene standards. Traveller's diarrhea, an orofecally transmitted disease, is certainly among those that most frequently affect travellers. It is characterised by variably intense diarrhea and a range of enteric symptoms, and is sustained by many different pathogens (bacteria, protozoa and viruses). It is reported to be one of the principal diseases arising

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during stays in developing countries (Shlim, 2005) and it is the cause of up to 50% of the travellers' requests for healthcare services (Al-Abri *et al.,* 2005). At the same time, cholera is considered a major public health problem in developing countries and an imported disease in developed countries. Clinically, it ranges from mild or moderate to severe disease, which has a high mortality rate. Primary prevention is fundamental for people visiting high-risk areas, and involves respecting the norms of correct personal and dietary hygiene (avoid contaminated water or food prepared using contaminated water). Recently, an oral anti-cholera vaccine became available, which also protects against traveller's diarrhea (Ryan and Calderwood, 2000). This vaccine, which stimulates the formation of serum and intestinal antibodies against cholera toxin (Scerpella *et al.,* 1996) is advisable for travellers who have to go to countries in which cholera has an endemic/epidemic pattern (Topps, 2006). The aim of this study was to assess the compliance to this new oral anti-cholera vaccine and the onset of adverse reactions in a group of international travellers visiting areas at risk of traveller's diarrhea.

MATERIALS AND METHODS

Between 2008 and 2009, the study involved subjects visiting areas at risk of cholera and traveller's diarrhea who were offered the possibility of immunization with the whole-cell recombinant B subunit inactivated oral anti-cholera vaccine (WC/rBS, Dukoral). The protocol foresaw the administration of two oral doses separated by a period of at least one week, to be taken at least seven days before travelling to areas at risk. It was asked to the vaccinated subjects to indicate the possible occurrence of adverse effects in the days following the vaccination. Each 3 ml dose contains $1x10^{11}$ heat- or formalin inactivated of the *Vibrio cholerae* O1 Inaba classic, *V. cholerae* O1 Inaba El Tor, and *V. cholerae* O1 Ogawa classic strains, and 1 mg of the recombinant cholera toxin B subunit (rCTB). Within few days after their return from abroad, they received a self-administered questionnaire including 40 mainly closed questions relating to their personal details and health (previous and current diseases, drugs), the trip (country, duration and reason) the appearance of gastrointestinal disturbances (duration, entity and effects limiting their normal activities), the anti-cholera vaccination, the onset of any adverse reactions. The questionnaires were collected at the Italian travel medicine centres of Ferrara, Agrigento, Reggio Calabria, Milano, Caserta, Paola, Lucca. The data were processed using StatView statistical software.

RESULTS

A total of 182 questionnaires were collected from 97 males, 84 females and 1 person of unspecified gender. The mean age was 39.3 years. The mean duration of the trips was 19.4 days. Most of the trips were for tourism (78.6%), 17.6% were reported as purposes of international cooperation, 3.8% as work. 87 of the travellers visited Africa, 61 Asia, 29 Central and Southern America, and 5 other Countries. Before the travel, 149 travellers did not report any disease, 27 indicated the presence of disease, 6 did not reply. At the time of departure, 45 subjects were receiving pharmacological treatment. After having been informed about the characteristics of the oral vaccine by the personnel of the travel medicine centres participating in the study, 123 subjects (67.6%) took the Dukoral vaccine correctly. No serious adverse events were reported, with a good compliance. During the trips, 17 immunised subjects (13.8%) reported the onset of diarrhea (more than 3 bowel movements/day). A total of 9 of these subjects defined the symptoms as mild, 6 as moderate and 2 as severe. A total of 5 subjects were prevented from carrying out their planned activities, 3 received medical care, but no one was hospitalised. A total of 11 (18.6%) unvaccinated subjects referred diarrhea: the symptoms were moderate or severe in 9 cases (81.8%).

DISCUSSION

The prevention of traveller's diarrhea is a priority for people travelling to highly endemic areas, and, in addition to more significant diseases, has a major epidemiological impact by significantly reducing normal activities when travelling (Al-Abri, *et al.* 2005). Preventing these diseases requires the adoption of precise behavioural rules and, when available, the use of safe and efficacious vaccination. A new whole-cell recombinant B subunit inactivated oral anti-cholera vaccine (WC/rBS, Dukoral) became available recently: this vaccine has also proved to be effective against the diarrhea caused by ETEC strains that produce thermolabile toxin (Jelinek and Kollaritsch, 2008). According to published data, the efficacy of Dukoral vaccine against cholera is more than 80% (World Health Organization, 2009). One of the particularly interesting findings of the present study is the percentage of subjects (67.6%) who accepted the vaccine after speaking with the physicians at the travel medicine centres. Fiftynine did not take it, although they were informed during pre-departure counselling: the reasons for the refusal were mainly personal. Overall compliance with the vaccination was satisfactory and there were no statistically significant

gender-related differences in accepting it (p=0.34). In the group of vaccinated travellers, the overall incidence of diarrhea was 13.8%, lower than the 17.4-23% reported in other recent studies demonstrating a 43-57% rate of vaccine efficacy against travellers' diarrhea (regardless of the causal agent), and an incidence of 39.7-40% among non-vaccinated subjects (Lopez-Gigosos *et al*., 2007; Torrell *et al*., 2009). Moreover, tolerability was more than satisfactory and in line with the findings of other studies. It is important to remember that the use of this vaccine in travellers going to areas at risk for cholera has also a good cost/efficacy ratio (Lundkvist *et al*., 2009). In this study the not vaccinated subjects, because of their small number, do not represent a real control group, and the related results should be considered cautiously. In conclusion, given its efficacy against cholera and traveller's diarrhea, the new oral anti-cholera vaccine (WC/rSB, Dukoral) is an interesting proposal for the prevention of major feco-oral diseases in travellers.

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High prevalence of Giardiasis in a Gipsy Roma Community in Verona, Italy

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Summary- The prevalence of intestinal parasites was assessed in a group of Roma children living in a Gipsy camp. The camp residents were very young, illiterate and experienced harsh conditions of discrimination, segregation and extreme poverty. Overcrowding and high number of children favored the spread of parasitic infections. A random sample of 27 children (mean age 4.5 years) were submitted to microscopic copro-parasitological examination (three samples per subject). Samples negative for *Giardia intestinalis* were also submitted to ELISA antigen test for this parasite. Seven protozoan and three helminth species were detected. We found an exceptionally high prevalence of *G. intestinalis* (22/27 or 82%). *Blastocystis hominis* was the second most frequently identified parasite. Multiple infections were detected in 21/27 subjects. Only one child (a still breast fed infant) had no detectable infection. We emphasize the need to know more of the health status of the Gipsy populations living in Europe. Our study is an indicator of an unacceptably low level of health and of the living standard of this community and of the urgent need to take serious initiatives in order to improve it.

Riassunto - E' stato effettuato uno studio della prevalenza delle parassitosi intestinali nei bambini di un campo rom, abitato da soggetti molto giovani, spesso analfabeti e sottoposti a condizioni di discriminazione, esclusione e povertà estreme. La diffusione delle parassitosi era favorita, tra l'altro, dal sovraffollamento e dall'elevato numero di minori. E' stato effettuato un esame microscopico copro-parassitologico su un campione scelto con criterio random di 27 bambini (età media 4,5 anni). I campioni risultati negativi per *Giardia intestinalis* sono stati sottoposti anche a ricerca dell'antigene giardia in ELISA. Sono state identificate sette diverse specie di protozoi e tre di elminti. E' stata riscontrata una prevalenza eccezionalmente elevata di *G. intestinalis* (22/27 o 82%), seguita da *Blastocystis hominis*. In 21/27 soggetti le infestazioni erano multiple. Solo nel caso di un bambino non ancora svezzato non si riscontrava alcuna infezione. Oltre a evidenziare la necessità di maggiori conoscenze sulla salute delle popolazioni rom presenti in Europa, questo studio conferma la persistenza di condizioni sanitarie ed esistenziali inaccettabili che impongono iniziative responsabili ed urgenti.

Key words: Intestinal parasites, *Giardia intestinalis, Blastocystis hominis*, Gipsy camp.

INTRODUCTION

Intestinal parasites are especially common in secluded and crowded communities, and particularly so in children (Thompson, 1994). Data on parasite prevalence in Gipsy communities living in Italy are lacking, despite the obvious risk of parasitic infections in people living in precarious hygienic conditions. A parasitological study on the prevalence of intestinal parasites was carried out on a group of Roma children living with their families in a Gipsy camp equipped by the Municipality of Verona. The study focused on children because of the distinctive structure of the demographic pyramid of the community (the vast majority of which was composed of very young subjects), and because children are particularly exposed to the clinical consequences of parasite infections.

BACKGROUND

History and structure of the Gipsy camp. After an uneven sequence of extremely precarious dwellings, a group of around 150 people (all Roma of recent emigration from southern Rumania, where they used to be permanent residents) reached, at the beginning of 2006, the city of Verona, Italy. They were sheltered by the Municipality of Verona in a structure specifically built to this purpose (the so called "Gipsy Camp of Boscomantico") located near the right bank of the Adige river and surrounded by a vast agricultural area.

The camp was situated on a public land of about one acre, surrounded by a fence, equipped with public utilities (two clusters of sanitary fittings, cookhouse, guard, room for recreational activities and surgery)

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and with 46 very basic single-family cabins (obtained from containers). Living and hygienic conditions were reasonably good. Electric power, lighting, hot and cold drinkable water supply and adequate environmental safety were provided.
Every family did its own cooking in the common kitchen. All people living in the camp, and children in particular, carried out an intense social life and, especially in winter, used to gather in narrow and crowded spaces.
In spite of the availability of an adequate number of lavatories, many children used to defecate in the open air, near the camp's inner borders, and during the hot season the children used to walk barefoot inside and outside the camp.
The socioeconomic situation of most families was very low and precarious and illiteracy was widespread.
The Municipality of Verona subscribed (September 27th, 2006) an agreement with the international voluntary health organization Medici per la Pace (Doctors for Peace) (www.mediciperlapace.org) for an intervention of hygienic and medical surveillance, prophylaxis and health protection for the camp settlers.
The activities went on uninterruptedly for 18 months, until the new authorities of the municipality decided to close the camp, at the end of March 2008. Activities included specialized medical examinations at least once a week; support to Local Socio-Sanitarian Unit (ULSS) 20 of the Veneto Region for immunizations; emergency medical interventions; continuous educational activity in the topics of hygiene, health and family planning; the implementation of epidemiological surveillance, including the prevalence of intestinal parasites in children.

Rationale of the study. A high prevalence of intestinal parasites could be expected on the basis of several considerations. First of all, historical reasons: families were coming from harsh conditions of poverty and social alienation already experienced in the country of origin, where they often lived in situations of discrimination, segregation and extreme deprivation, sometimes almost literally starving. In second place, cultural reasons: the camp residents were in large majority more or less illiterate and seemed to ignore many basic hygienic rules. Many other factors such as the high number of children, the overcrowding and the close sharing of most aspects of social life were supposed to potentially favour the spread of parasitic diseases.

POPULATION AND METHODS

Study population. When we started our medical intervention (October 1st, 2006) a total of 145 people (67 males and 78 females, sex ratio 0.85) were living in the camp.
They were grouped in 29 families, with a mean of 5 components each.
The typical family was composed of a couple of very young parents, an unweaned baby and other children. Adults were very few. The marital unions, mostly not formalized, were contracted by teen agers; the pregnancies were premature, numerous and not spaced. The mean age was 14.5 years, 13.4 years for males (representing 46% of the whole population, the oldest one being 51 years old) and 15.4 for females (54% of the whole population, the oldest one being 50 years old). The population younger than 6 years represented more than one third (37%, with a preponderance of males) while the population older than 30 years represented less than one tenth (8%, mostly females) of the total. All the camp guests had the same place of origin and nobody reported any previous stay in tropical regions.
Sampling. Among the children living in the camp, we excluded from the study the newborns and infants less than one year old, who, as a rule, were all still breast-fed. Of the remaining 57 children of both sexes, aged between 1 and 12 years, we randomly sampled 27 children (47%): the mean age was 4.5 years. After obtaining the parents' informed consent, three formalin preserved fecal samples were collected from each child on alternate days.
Laboratory testing. Specimen were submitted to formalin - ether concentration according to Ritchie as modified by Buonomini *et al*. (1957) and then examined by two skilled microscopists of a reference Italian laboratory. Each sample was first examined at 100 x for helminth ova or larvae, then at 400 x for protozoa. Microscopically negative samples for trophozoites or cysts of *Giardia intestinalis* were also submitted to ELISA antigen test for *G. intestinalis* (CELISA detection kit, Cellabs).

RESULTS

On the whole, seven protozoan species (*Giardia intestinalis, Entamoeba histolytica/dispar, Entamoeba coli, Entamoeba hartmanni, Iodamoeba butschlii, Endolimax nana* and *Blastocystis hominis*) and three helminth species *(Hymenolepis nana, Trichuris trichiura* and *Enterobius vermicularis*) were identified in the study population. The results are summarized in Table 1.
The findings of individual subjects are reported in Table 2.
Multiple infections were detected in 21 cases: 7 quadruple infections (26% of the total of studied subjects), 11 triple infections (41%), and 3 double infections (11%). Five subjects had a single infection (*G. intestinalis* in 4/5). In only one case (4%)

were both microscopy and antigen detection negative (Fig. 1).

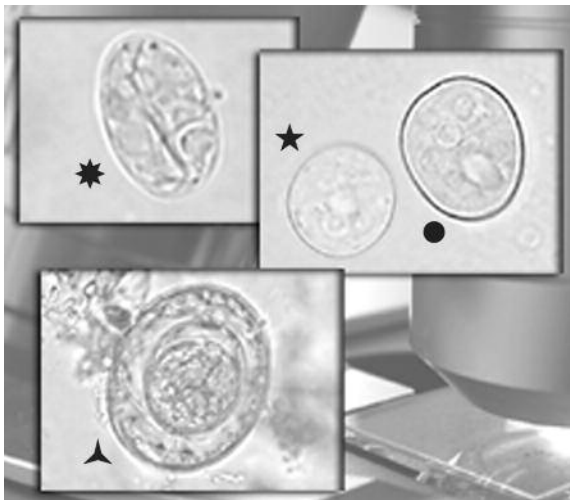

Figure 1 - Multiple infection (subject N. 14). Microscopic aspect of cysts of ✸G. intestinalis, ★E. histolytica/dispar, ●E. coli and of eggs of ⅄H. nana (size not proportional).

Table 1 - Parasites identified

Species	N. subjects infected	%
Giardia intestinalis	22	82
Entamoeba histolytica/dispar	6	22
Blastocystis hominis	15	56
Entamoeba coli and/or E. hartmanni	14	52
Iodamoeba butschlii	1	4
Endolimax nana	3	11
Hymenolepis nana	10	37
Trichuris trichiura	1	4
Enterobius vermicularis	1	4

DISCUSSION

All children in the sample had parasite infections (multiple infections in most cases), with the exception of one (N. 11, thirteen months old), who was the youngest of the group and still breast-fed. We found an exceptionally high prevalence of *G. intestinalis* (22 cases, or 82% of the total).

G. intestinalis is a flagellate enteric protozoan belonging to the Family *Hexamitidae*, Order *Diplomonanida*. It is a pathogen of human as well as

Table 2 - Parasites identified per individual subject

Subject	Birth Year	Gi	Ec	Eh	En	Ib	Bh	Hn	Tt	Ev
1	2005	X*		X			X			
2	2004	X	X	X						
3	2005	X					X	X		
4	2006	X					X	X		
5	2006	X								
6	2005	X					X	X		
7	2003	X	X	X						
8	2004		X		X			X		
9	2004	X	X				X			
10	2006	X				X	X			
11	2006									
12	2002	X	X				X			
13	2002						X			
14	1998	X	X	X				X		
15	2005		X							
16	2003	X	X							
17	2005	X								
18	1996	X	X		X		X			
19	1999	X	X		X		X			
20	2001	X	X				X	X		
21	2002	X	X				X			
22	2006	X						X		
23	2006	X		X				X	X	
24	2000		X				X			X
25	2006	X								
26	2004	X		X			X	X		
27	2001	X	X				X	X		

Legenda: Gi: *Giardia intestinalis;* Ec: *Entamoeba coli* and/or *hartmanni*; Eh: *Entamoeba histolytica/dispar* ; En: *Endolimax nana*; Bh: *Blastocystis hominis* ; Id: *Iodamoeba butschlii*; Hn: *Hymenolepis nan*; Tt: *Trichiuris trichiura* ; Ev: *Enterobius vermicularis*

*Antigenic search positive for *Giardia intestinalis*

of other mammalian species (canids, cats, rodents etc.). *G. intestinalis* is considered one of the more relevant pathogenous intestinal parasite causing diarrhea and malabsorption (Adam, 2001). It is transmitted through person to person oro-fecal diffusion or it is ingested with contaminated food or water (Mintz *et al*., 1993). This protozoon has a wide distribution all over the world and represents one of the most frequent human intestinal parasites. It is rare during the first semester of life, particularly in breast-fed babies, but its prevalence grows from childhood to adolescence, with a reduction in the youth and a further increase during the third decade of adult life. Its prevalence varies from 2% to 5% in developed countries. *G. intestinalis* represents the most frequently isolated intestinal parasite in the USA (Olsen *et al*., 2000), while its prevalence in children <10 years old in developing countries is held to amount to 30% (Gilman *et al*., 1985). The most frequent form of giardiasis is that of asymptomatic carrier (*G. intestinalis* being symptomatic in less than one half of cases, from 20% to 50%). Diarrhea, the main symptom, becomes persistent in 30-50% of symptomatic patients and is often associated with steatorrhea. In children less than 5 years old, it may cause dehydration, malabsorption and related growth and development defects. The consequent malnutrition, in its turn, may predispose to parasitic infection, creating a vicious circle.

In Italy, as well as in other developed countries, *G. intestinalis* is more often diagnosed in subjects, mainly children, coming from endemic areas, and/or living in enclosed communities. In children institutions, a similar prevalence to that of tropical countries is sometimes found.

The main diagnostic tool for giardiasis is the coproparasitological examination, with a diagnostic specificity of 100% and a sensitivity of >90% (when done on at least three samples collected in different days).

The striking prevalence of parasite infections, and of *G. intestinalis* in particular, found in our study sample may be explained by several causes:

a) the origin of the study subjects from a country (where they frequently return for short stays) with higher prevalence than Italy;
b) the peculiar demography of the camp, with high prevalence of very young subjects;
c) the camp characteristics (a close and institutional-like structure);
d) the high density of the camp population;
e) the general unavoidable promiscuity, particularly in the food preparation in the cookhouse;
f) the low level of hygiene and health awareness and education;
g) the situation of extreme poverty and social alienation suffered by the whole community.

Even in a rich and industrialized country like Italy, the cultural, social and economic conditions, rather than the pathogenic agents, are once more the real determinants of the diseases prevalence.

Because of the almost generalized presence of this pathogen, and the difficulty in examining the whole population of the camp, we decided, with the support of the Local Socio-Sanitarian Unit (USSL 20 of Verona), to treat for giardiasis the whole child population of the camp (Fig. 2).

Figure 2 - Life in the camp.

After giardia, *Blastocystis hominis* was the second most frequently identified parasite.

The prevalence of *B. hominis* in this specific pediatric population (56%) was not only five to thirty times higher than that usually found in western countries, but even higher than the mean prevalence reported in developing countries (Tan *et al*., 2002). It is difficult, because of so many multiple infections, to correlate a possible pathogenic effect of *B. hominis*, that is a still debated subject in the medical literature (Doyle *et al*., 1990; Windsor *et al*., 2002). *B. hominis* was diagnosed as an isolated infection in just one case: the patient, a 4-year-old girl, was asymptomatic.

CONCLUSIONS AND RECOMMENDATIONS

We believe that our study emphasizes the need to know more of the health status of the Gipsy populations living in Europe. Italy is a country whose Constitution specifically declares the right to health of every individual, and our current laws favour the access of everybody to health care. Nevertheless this right is often only theoretical for part of the immigrant population and also for those who are European citizen at all effects, such as the Gipsy (Roma) communities coming from Rumania. A common policy vis-à-vis the Gipsy populations is still lacking in Europe, and of course this is a complex problem that involves political, sociological and anthropological considerations rather than barely medical aspects. Nevertheless, we believe that our small study should be taken as an indicator of an unacceptably low level of health and of the living standard of this community and of the urgent need to take serious initiatives in order to improve it.

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