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LECTURE NOTES ON TROPICAL MEDICINE AND GLOBAL HEALTH



a cura di:

Maria Grazia Bedetti, Silvio Caligaris, Federico Gobbi, Marianne Strohmeier

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A CURA DI:

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**DIPARTIMENTO DI MALATTIE INFETTIVE/TROPICALI E MICROBIOLOGIA, IRCCS SACRO CUORE - DON CALABRIA,
NEGRAR DI VALPOLICELLA, VERONA**

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PREFAZIONE

Questo 5° numero della collana “**Quaderni di Medicina Tropicale e Salute Globale**” edito dalla Società Italiana di Medicina Tropicale e Salute Globale (SIMET), è dedicato alla raccolta di contributi prodotti da una parte dei docenti del Master Italiano di Medicina Tropicale e Salute Globale su alcuni dei maggiori temi di salute globale.

Il Master Italiano di Medicina Tropicale e Salute Globale rappresenta un’offerta formativa diretta a personale sanitario in possesso di laurea triennale o magistrale ed è realizzato, a partire dall’anno accademico 2012/2013, dalle Università di Brescia e Firenze, con la collaborazione del Centro di Medicina Tropicale dell’Ospedale Sacro Cuore Don Calabria di Negrar (VR).

Dopo qualche anno di attività, su proposta del *Past President* di SIMET, Professor Francesco Castelli, è stato chiesto ad alcuni docenti di produrre un articolo relativo al tema da loro affrontato all’interno del Master, ottenendo una risposta positiva da ognuno di loro. La pubblicazione, oltre a rendere fruibili le lezioni agli studenti del Master, così come a quelli del Corso di Perfezionamento di Malattie Tropicali e Medicina Internazionale realizzato a Brescia e del Corso di Perfezionamento di Medicina Tropicale Cooperazione Internazionale svolto a Firenze, rappresenta un’opportunità di aggiornamento per chiunque sia interessato alle tematiche trattate.

La raccolta dei testi è stata coordinata dal Dr. Silvio Caligaris, coadiuvato dal Dr. Federico Gobbi e dalla Dott.ssa Marianne Strohmeier. L’attenta gestione dei contributi fino alla loro definitiva pubblicazione si deve alla segretaria della SIMET, Sig.a Maria Grazia Bedetti.

L’uscita di questo numero ha subito un ritardo rispetto al previsto in conseguenza dell’inattesa pandemia dovuta a SARS-CoV-2 che con i suoi effetti diretti e indiretti ha prodotto sofferenze e vittime tra la popolazione di ogni continente, messo a dura prova i sistemi sanitari e ha reso ancora una volta evidente come ingiustizia e disuguaglianze siano i principali determinanti della salute.

La pubblicazione in forma cartacea è stata resa possibile grazie ai contributi ricevuti dalla Cattedra UNESCO “*Training and empowering human resources for health development in resource-limited countries*”, diretta dal Prof. Francesco Castelli e dalla Società Italiana di Malattie Infettive e Tropicali (SIMIT), presieduta dal Dr. Marcello Tavio. A entrambi va il mio personale ringraziamento, per il fondamentale sostegno.

Durante il 2020, SIMET ha dovuto affrontare anche il lutto per la scomparsa del Prof. Giancarlo Majori. Il Prof. Giancarlo Majori ha contribuito in maniera eccellente alla ricerca scientifica in campo malariologico e più in generale nell’ambito della sanità pubblica italiana. E’ stato Direttore del Laboratorio di Parassitologia dell’Istituto Superiore di Sanità e del Collaborating Centre WHO sulle Malattie Tropicali Neglette. Il Prof. Majori è stato per tutti noi un punto di riferimento scientifico e sicuramente il ruolo da lui svolto come Presidente della SIMET è stato fondamentale quanto indimenticabile.

Oltre a beneficiare della sua illuminata guida della SIMET abbiamo potuto approfittare dei suoi insegnamenti, dei suoi consigli, del suo entusiasmo.

A lui intendiamo dedicare questo numero dei Quaderni.

Prof. Alessandro Bartoloni
Presidente, Società Italiana di Medicina Tropicale e Salute Globale (SIMET)

This 5th issue of the series “**Quaderni di Medicina Tropicale e Salute Globale**” published by the Italian Society of Tropical Medicine and Global Health (SIMET), is dedicated to the collection of contributions produced by a part of the teachers of the Italian Master of Tropical Medicine and Global Health on some of the major global health issues.

The Italian Master in Tropical Medicine and Global Health represents a training offer aimed at healthcare personnel

with a three-year or master's degree and is carried out, starting from the 2012/2013 academic year, by the Universities of Brescia and Florence, with the collaboration of Tropical Medicine Center of the Sacro Cuore Don Calabria Hospital in Negrar (VR).

After a few years of activity, on the proposal of the *Past President* of SIMET, Professor Francesco Castelli, some teachers were asked to produce an article on the topic they tackled within the Master, obtaining a positive response from each of them. The publication, in addition to making the lessons available to the students of the Master, as well as to those of the Postgraduate Course in Tropical Diseases and International Medicine held in Brescia and the Postgraduate Course in Tropical Medicine International Cooperation held in Florence, represents an opportunity to update for anyone interested in the topics covered.

The collection of texts was coordinated by Dr. Silvio Caligaris, assisted by Dr. Federico Gobbi and Dr. Marianne Strohmeier. The careful management of the contributions until their final publication is due to the SIMET secretary, Ms. Maria Grazia Bedetti.

The release of this issue has been delayed, compared to expected, as a result of the unexpected pandemic due to SARS-CoV-2 which with its direct and indirect effects has produced suffering and victims among the population of every continent, put to the test health systems and has made it clear once again that injustice and inequality are the main determinants of health.

The paper publication was made possible thanks to the contributions received from the UNESCO Chair "*Training and empowering human resources for health development in resource-limited countries*", directed by Prof. Francesco Castelli and by the Italian Society of Infectious and Tropical Diseases (SIMIT) , chaired by Dr. Marcello Tavio. My personal thanks go to both of them for their fundamental support.

During 2020, SIMET also had to face mourning for the disappearance of Prof. Giancarlo Majori. Prof. Giancarlo Majori has made an excellent contribution to scientific research in the malariology field and more generally in the Italian public health sector. He was Director of the Parasitology Laboratory of the Higher Institute of Health and of the WHO Collaborating Center on Neglected Tropical Diseases. Prof. Majori was a scientific reference point for all of us and certainly the role he played as President of SIMET was as fundamental as it was unforgettable.

In addition to benefiting from his enlightened leadership of the SIMET, we were able to take advantage of his teachings, his advice, his enthusiasm. We intend to dedicate this issue of the Quaderni to him.

Prof. Alessandro Bartoloni
President, Italian Society of Tropical Medicine and Global Health ((SIMET)



PREFAZIONE

La Cattedra UNESCO *Training and empowering human resources for health development in resource-limited Countries* è stata istituita nel 2014 presso la Università di Brescia in virtù della lunga tradizione formativa che la stessa Università di Brescia ha svolto e continua a svolgere nel settore della formazione del personale sanitario sia italiano che straniero che opera nei Paesi a risorse limitate.

La Cattedra UNESCO promuove il Corso di Perfezionamento in Salute Globale della Università di Brescia, Corso Base del Master Europeo TropEd in Salute Internazionale (www.troped.org) e componente del Master italiano interuniversitario in Medicina Tropicale e Salute Globale.

Tra le varie attività della Cattedra UNESCO della Università di Brescia, oltre alla erogazione di Borse di Studio per la frequenza al Corso di Perfezionamento in Salute Globale della Università di Brescia ed alla promozione dei valori generali di UNESCO con specifico riferimento alla promozione della Cultura, della Scienza e della Educazione soprattutto nei Paesi a risorse limitate, la formazione degli operatori sanitari nei contesti di marginalità e disuguaglianza assume un posto prioritario.

E' dunque con grande piacere, nel solco del proprio mandato statutario, che la Cattedra UNESCO della Università di Brescia ha deciso di contribuire, promuovere e sostenere questa pubblicazione della Società Italiana di Medicina Tropicale e Salute Globale (SIMET), finalizzata a servire come base per lo studio delle principali tematiche dello sviluppo nei contesti dove la scarsità di risorse comporta ancora la disuguaglianza nell'accesso ai servizi sanitari, con l'obiettivo finale di contribuire al raggiungimento degli Obiettivi di Sviluppo Sostenibile fissati dalle Nazioni Unite per il 2030.

Brescia, 20 giugno 2020

Prof. Francesco Castelli, MD, FRCP (London), FFM RCPS (Glasg), FISTM, FESCMID

Professore Ordinario di Malattie Infettive, Università degli Studi di Brescia

Pro-Rettore Vicario, Università degli Studi di Brescia

Cattedra UNESCO *Training and empowering human resources for health development in resource-limited Countries*

Past-President, Società Italiana di Medicina Tropicale e Salute Globale (SIMET)

The UNESCO Chair *Training and empowering human resources for health development in resource-limited Countries* has been established at the University of Brescia in 2014, as a recognition of the long-standing tradition of the University of Brescia in training health personnel, both Italian and foreigner, on the critical topics of global health with particular regard to low-middle income Countries.

The UNESCO Chair promotes the post-Graduate Course in Global Health at the University of Brescia, that is Core Course of the TropEd European Master in International Health (www.troped.org) and structural component of the inter-University Italian Master in Tropical Medicine and Global Health.

Among the various activities of the UNESCO Chair, besides offering Scholarships to attend the post-Graduate Course

in Global Health and the promotion of the cultural, scientific and educational values of UNESCO, the training of health workers in social contexts of marginalization, inequity and poverty is a priority and crucial task.

It is then a pleasure for me, in line with the statutory mandate of the UNESCO Chair, to promote and support this timely publication of the Italian Society of Tropical Medicine and Global Health (SIMET).

I hope that this Lecture Notes will serve as a guide to study the main topics of development and health in those contexts where scarcity of resources make access to health services inequitable, with the final aim to contribute to the achievement of the Sustainable Development Goals of the UN 2030 Agenda

Brescia, 20 June 2020

Prof. Francesco Castelli, MD, FRCP (London), FFTM RCPS (Glasg), FISTM, FESCMID

Professor of Infectious Diseases, University of Brescia

Deputy Rector, University of Brescia

UNESCO Chair Training and empowering human resources for health development in resource-limited Countries

Past-President, Italian Society of Tropical Medicine and Global Health ((SIMET)

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Global Health and Globalization

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1. The origin of global health

The term *global health*, and the concept behind it, was derived from those of *public health* and *international health*. The first was born in the 19th century, from the encounter of the new social reform movements and the advances in the biological and medical fields, where the latter finds its origins in tropical medicine, and it was used in referral to health concerns in developing countries, mostly taking care of infectious and tropical diseases, child and maternal health, malnutrition, water and sanitation.

The start of International health cooperation is settled in 1851, during the first International Sanitary Conference in Paris, when European states met to discuss cooperation on cholera, plague, and yellow fever. The aim of this conference was to reach an agreement among the different European nations, in order to reduce the several existing maritime quarantine requirements. During the second half of the 19th century, quarantines were indeed the only system that countries had to deal with transboundary disease transmission. This produced great costs on the trade of goods, which led to an increasing pressure for the achievement of an international pact for the reduction of quarantines [1]. After this, several other conferences were held, leading to the first international sanitary convention on cholera on 1892, and on prevention of plague in 1897.

By the end of 1908, two international sanitary societies existed: the International Sanitary Bureau in the American republics, existing since 1902, and the Office International d'Hygiène Publique (OIHP), born in 1907. During the second World War, the works of the international health agencies came to a stalemate, but after that, in 1948 the World Health Organization (WHO) started to exist [2].

With the establishment of the WHO, international health was embodied by a supranational agency, aiming to lead an impartial technical cooperation with the objective of worldwide improvement and development of health. WHO mandate included: standard-setting, data collection, epidemiologic surveillance, training of health workers and research, emergency relief, and cooperative activities. In 1978, WHO reached two big achievements: smallpox eradication and the Declaration of Alma Ata, which for the first time declared primary health care as the key for the attainment of the goal of "**Health for All**" around the globe [3]. In recent years, funding shortages and structural and organizational difficulties hampered WHO works. Newer global health agencies and organizations emerged on the international scene in the last years, such as the World Bank and the Bill and Melinda Gates Foundation, the United Nations Joint Programme on HIV/AIDS, the Global Alliance for Vaccines and Immunization, UNITAID, the Global Fund to Fight AIDS, Tuberculosis and Malaria and several Non-governmental organizations (NGOs).

Nowadays, many decisions about global health are made outside the WHO, and a call for a greater coordination between the several stakeholders acting on the global health scenario is needed, in order to reach the ambitious objective of "Health for all".

2. Global health and globalization

Globalization - *the emergence of a world marketplace of goods, services, capital, people, and ideas* - is a defining economic and social trend of the past several decades [4]. It has been defined as a process, where the increasing and easier interconnections between faraway countries lead to the fact that an event happening in one part of the world, may have effects on countries, people and systems on the opposite side of it. Although we started talking about globalization only recently, this idea is not new to historians. Indeed, phenomena such as immigration, travel, trade, war and infectious diseases have been characterizing humankind since its origins [1]. In the past years plague, flu, smallpox or cholera epidemics as well as nowadays acute respiratory syndrome (SARS), H1N1 influenza pandemic, Zika and Chikungunya viruses outbreaks and the Ebola virus epidemic, clearly showed us how diseases can spread widely, without considering national and international borders.

*The Author is responsible for the views contained in this article and for opinion expressed therein, which are not necessarily those of UNESCO and do not commit the Organization.

Moreover, connections become every day easier and faster, highlighting the increasingly transnational nature of health debate [4]. Other aspects of globalization also affected global health in less visible ways, such as the inequity of access to the health care system generated by international “medical tourism”, due to the employment of doctors in private institutions rather than in the public ones, and the migration of health practitioners trained in developing settings towards richer countries [4]. Global health reflects the realities of globalization, especially in view of the challenges related to the increased exchange of either people and goods, to the consequent faster spread of infectious diseases and to the shifting epidemiology of non-communicable diseases. As long as no nation can assure health to its people on its own, global health is in charge to guarantee and deliver essential care and to protect health of the entire global community [5].

3. What is global health?

Where several definitions have been given, Koplan *et al* in 2009 described global health “*as an area for study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasizes transnational health issues, determinants, and solutions; involves many disciplines within and beyond the health sciences and promotes interdisciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care*” [6].

Global health is, for its nature, multidisciplinary. Infectious and tropical diseases still play an important role in global health agenda, but new needs have arisen and affect people worldwide, and have to be taken into account. In the same way, traditional indicators of public health campaigns, such as maternal and infant mortality rates are no longer able to describe the health status of whole societies. According to De Cock [5], three interdependent macro-areas of work mainly characterize global health action: development, security, and public health.

3.1 Development

There is a clear correlation between a country income and its health indicator, such as infant death rates and life expectancy. This is obvious, if we consider that higher incomes guarantee basic hygiene standards such as potable water, sanitation and food security, as well as a better nutritional status, mother and child interventions and higher degrees of education among the population. Therefore, the main objective of development agencies must be poverty reduction.

3.2 Public health

In recent years, specifically targeted initiatives, such as those on HIV, malaria or vaccines, led to a certain disease-specific success. Nevertheless, these experiences also highlighted the lack of prioritization and the inattention to the other problems and needs of a specific population, thus failing in strengthening health systems in the area of intervention.

These perceptions led to the concept of seeing health needs in a more integrated manner and has been taken into account in the new Millennium Development Goals (MDGs).

3.3 Health security

The events of the last years reminded us that infectious diseases are far away from being defeated and that the spread of new and old pathogens can occur more and more rapidly through countries and continents. Therefore, health security must involve other sectors than health systems, such as defense and diplomacy, linkage with other international agreements, such as those relating to control of chemical, biological, and nuclear weapons, surveillance and laboratory capacity and, above all, a supportive and collaborative global health network.

The Sustainable Development Goals (SDGs) of United Nations

In 2015 all United Nations Member States adopted the 2030 Agenda for Sustainable Development, which provides a shared blueprint for peace and prosperity for people and the planet, now and into the future. At its heart are the 17 Sustainable Development Goals (SDGs), which are an urgent call for action by all countries - developed and developing - in a global partnership. They recognize that ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth - all while tackling climate change and working to preserve our oceans and forests.

The SDG 3 aims to “ensure healthy lives and promote well-being for all at all ages”. It encompasses:

1. By 2030, reduce the global maternal mortality ratio to less than 70 per 100,000 live births
2. By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births
3. By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat

- hepatitis, water-borne diseases and other communicable diseases
4. By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being
 5. Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol
 6. By 2020, halve the number of global deaths and injuries from road traffic accidents
 7. By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes
 8. Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all
 9. By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination
- a. Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate
 - b. Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all
 - c. Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States
 - d. Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risk [7].

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Sustainable Development Goals

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BACKGROUND

Health for all

Between September 6th and 12th, 1978, the declaration of the Alma Ata Conference called the international community for an urgent commitment to protect and promote health for all peoples in the world. The final goal was to establish a "New International Economic Order" able to fill the gap between developed countries and developing countries. [1]

A life of dignity for all

Twenty-two years later, on September 2000, the United Nations presented the Millennium Development Goals (MDGs). The MDGs motto was directed to the international community stating that "*spare no effort to free our fellow men, women and children from the abject and dehumanizing conditions of extreme poverty*". Overall, the MDGs have undoubtedly contributed on focusing the international attention and assistance towards the South of the world to face the extreme and serious poverty, with a specific emphasis on health aspects [2].

MDGs on Health

The first goal of the MDGs was focused on eradicating the extreme poverty and hunger.

In the health sector, although the objectives have not been completely achieved, significant progress has been made in decreasing child mortality (target: 2/3 of reduction compared to the 1990 values, conventionally considered the baseline), maternal mortality (target: 3/4 of reduction compared to the 1990) and the fight against endemic infectious diseases such as HIV, tuberculosis and malaria.

With regard to child mortality (Objective 4), the number of deaths in children under 5 years old decreased from 12.7 million in 1990 to 6 million in 2015, moving from a rate of 90 per thousand live births to 43 per thousand live births. In Southern Asia, the maternal mortality (Objective 5) ratio declined by 64 per cent between 1990 and 2013, and in sub-Saharan Africa it fell by 49 per cent. This is largely due to the increase of the proportion of pregnant women who received antenatal visits, moving from 59% in 1990 to 71% in 2014. However, the overall rate of assisted births is still 56% at the rural level, especially in the African continent where only 32% of the births are attended by skilled health personnel [2].

Yet inequalities in data availability on maternal health hamper efforts to guide establishment of priorities on national, regional and global health. The availability of data varies widely by region. More than 90 per cent of countries in Latin America have nationally representative data on maternal cause of death compared to less than 20 per cent of sub-Saharan African countries. Large inequities remain in maternal health, along with gaps in access to and use of sexual and reproductive health services that must be consistently addressed and monitored [2].

The fight against the main infectious diseases such as HIV/AIDS, malaria and tuberculosis (Objective 6) has also led to remarkable successes. The introduction of anti-HIV therapy is a concrete reality in almost all the countries worldwide, although data of rural areas reveal insufficient and greatly uneven progress, which however led to the decrease of the overall annual deaths from over 2 million in 2005 to a million in 2016 [3]. Even though this is good achievement, only 36 per cent of the 31.5 million people living with HIV in developing regions were receiving ART by 2013. Sub-Saharan Africa has both the largest share of people living

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*The Author is responsible for the views contained in this article and for opinion expressed therein, which are not necessarily those of UNESCO and do not commit the Organization.

with HIV and the largest increase in the number of people receiving ART. Despite that, Sub-Saharan countries registered also 78 per cent of the people living with HIV who are not receiving ART [2].

New HIV infections fell by approximately 40 per cent between 2000 and 2013, from an estimated 3.5 million cases to 2.1 million.

Since the global malaria incidence and mortality rates have fallen respectively of 37% and 58%, the MDG malaria target has been completely achieved. Malaria is still endemic in 97 countries around the world and the 80% of global malaria deaths occur in just 17 countries, mostly in Africa. Moreover, despite the great achievement, the implementation of diagnostic testing and treatment has been slower than expected, only 20 per cent of children with fever in sub-Saharan Africa receive a malaria diagnostic test.

The incidence rate of tuberculosis has been reduced by 1.5% each year, with a significant reduction in the number of deaths which remains still too high, around 1 million/year. Globally, the number of people receiving tuberculosis treatment grew from 2.9 million in 1995 to 5.8 million in 2012. [2]

The Sustainable Development Goals

On September 2015 the United Nations launched the 2030 Agenda for new global Sustainable Development Goals (SDGs), organized in 17 Goals and 169 targets that all the 191 UN Member States have agreed to achieve by the year 2030 [4]. Health has a central place in SDG 3: Ensure healthy lives and promoting well-being for all at all ages, underpinned by 13 targets. The 2030 Agenda proposes a strong generational alliance by involving present generations to preserve the planet for future generations. The definition of sustainable development is defined as the process capable to ensure *"the satisfaction of the needs of the present generation without compromising the ability of future generations to satisfy their own"* [5].

The macro-goals set by Agenda 2030 can be summarized by the so called five "Ps":

People

SDGs are determined to end poverty and hunger, in all their forms and dimensions, ensuring that all human beings can fulfil their potential in dignity and equality and in a healthy environment.

Planet

The planet should be protected from degradation taking urgent action on climate change, so that it can support the needs of the present and future generations.

Prosperity

The economic, social and technological progress should occur in harmony with nature, so that all human beings can enjoy prosperous and fulfilling.

Peace

There can be no sustainable development without peace and no peace without sustainable development.

Partnership

SDGs are based on a spirit of strengthened global solidarity, focused in particular on the needs of the poorest and most vulnerable and with the participation of all countries, all stakeholders and all people.

There are some major differences between MDGs and SDGs. The MDGs had a specific focus on developing countries with funds coming from rich countries. Instead, in the Agenda 2030 all countries, developed or developing, are expected to work towards achieving the goals. Another important difference recorded in the declaration of the SDGs, is the participation of numerous actors who actively collaborated in the drafting of the final document: civil society organizations, citizens, scientists, academics, and the private sectors from around the world were all actively engaged in the process. Moreover, the pillars of human development, human rights and equity are deeply rooted in SDGs and several targets explicitly refer to people with disabilities, people in vulnerable situations and non-discrimination. SDGs have one comprehensive goal emphasizing well-being and healthy living including NCDs (Non Communicable Diseases). The MDG instead had 3 direct health goals, with specific emphasis on child, maternal mortality and communicable diseases. [6]

The Goal n. 3 in the SDGs (*Ensuring health and well-being for everyone and for all ages*) is extremely challenging and ambitious. The first 3 targets are basically the updated revision of the Millennium Development Goals n. 4 (infant mortality), n. 5 (maternal mortality) and n. 6 (fight against the great infectious endemics), in order to finally reach them completely. Target 3.4 is directed towards non-infectious diseases, once almost exclusively owned by industrialized countries but now largely prevalent (especially obesity, diabetes and hypertension) even in low-income countries [7]. Subsequent targets place emphasis on substances of abuse (target 3.5), deaths and injuries caused by road accidents (3.6), sexual and reproductive health (3.8) and

Sustainable Development Goals	
GOAL 1	End poverty in all its forms everywhere
GOAL 2	End hunger, achieve food security and improved nutrition and promote sustainable agriculture
GOAL 3	Ensure healthy lives and promote well-being for all at all ages
GOAL 4	Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
GOAL 5	Achieve gender equality and empower all women and girls
GOAL 6	Ensure availability and sustainable management of water and sanitation for all
GOAL 7	Ensure access to affordable, reliable, sustainable and modern energy for all
GOAL 8	Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
GOAL 9	Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
GOAL 10	Reduce inequality within and among countries
GOAL 11	Make cities and human settlements inclusive, safe, resilient and sustainable
GOAL 12	Ensure sustainable consumption and production patterns
GOAL13	Take urgent action to combat climate change and its impacts[a]
GOAL 14	Conserve and sustainably use the oceans, seas and marine resources for sustainable development
GOAL 15	Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
GOAL 16	Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
GOAL 17	Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development

pollution health damage (3.9). In the Objective 3, four strategic points (3.a - 3.d) are strongly addressed towards developing countries, with emphasis for research in the field of drugs and vaccines and for the need of funds for health care and health personnel training.

The health is declined in the SDGs as following:

1. Reduce the global maternal mortality ratio to below 70/100,000.
2. Reduce neonatal mortality to below 12/1,000 and U5MR to below 25/1,000.

3. End the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases.
4. Reduce by one-third premature mortality from noncommunicable diseases.
5. Strengthen the prevention and treatment of substance abuse.
6. Halve the number of global deaths and injuries from road traffic accidents (by 2020).
7. Ensure universal access to sexual and reproductive health-care services.
8. Achieve universal health coverage.
9. Reduce the number of deaths and illnesses from hazardous chemicals and air, water, and soil pollution and contamination.

Maintaining peace is essential for development. A threat for the international peace and stability is emerging as a major factor for both developed and developing countries. For instance, the recent crisis in Syria has forced 12 million people to leave their homes and made them refugees.

Since the declaration of the MDGs, the number of international migrants has increased by around one third, today reaching 244 million. Migration is a mega-trend of the twenty-first century, with considerable impact on all three dimensions of sustainable development. Currently, most migration occurs through safe and regular means. The majority of the world's international migrants leave from, transit through and move to countries of destination without incident. However, this is not the case for all migrants, many of whom experience significant discrimination, lack of opportunity, and exploitation. While the 2030 Agenda for Sustainable Development recognizes the "*positive contribution of migrants for inclusive growth and sustainable development*," it also recognizes that migrants' energy and ingenuity is often squandered. In order to tackle the issue of migration for sustainable development, the SDGs clearly urge countries to implement "*planned and well-managed migration policies*". Unfortunately, the IOM (International Organization for Migration) has repeatedly witnessed the failure of one-dimensional border-control policies, or worse, "no policy at all." [8] The Agenda 2030 has opened on the horizon a new and engaging challenge, through which the entire human being has the duty and the moral obligation to take part, since we are all equally and ineluctably involved.

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From Alma-Ata to nowadays: ups and downs of Primary Health Care

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In 1946, the member states of the newly formed United Nations gathered in New York to draft and sign the constitution for the World Health Organization (WHO). “The attainment by all peoples of the highest possible level of health” was set as the objective of the new organization. Health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [1] was identified as a fundamental human right. Implicitly, promoting good health could not be achieved through medical care alone, nor solely through the control of diseases, but would, instead, require a much wider and intersectoral approach.

Despite its holistic definition of health, “vertical” disease control and eradication programs characterized the global health policy until nowadays, starting with the large-scale treatment of syphilis, and the malaria and smallpox eradication programs in WHO’s early years of activity.

During the 1950s, the international development agenda was heavily by the Modernization Theory, elaborated by American economists, assuming that industrialization and mass-consumption driven economic-growth would lead to DC’s “takeoff” and that in the long run the “trickle-down effect” would spread modernization from urban to rural areas.

The foundations of the classical development theory were criticized in the following decades. In the 1970s, the debate was fueled by the Movement for the New International Economic Order (NIEO) and the so-called “basic needs” approach. Indeed, despite the positive overall economic performance of the Third World, growth failed to alleviate poverty. In that context the WHO shifted towards strategies more attentive to the development of basic health services, community participation, and the immediate health needs of the population.

Under the leadership of the Danish Director-General of the WHO Halfdan Mahler, in 1977, the World Health Assembly (WHA) adopted the goal of “Health for all by the year 2000” and the following year, with the Declaration of Alma-Ata, Primary Health Care (PHC) was identified as the best strategy toward that objective [2].

PHC was viewed not only as an integral part of each country’s health system, but also as important for the social and economic development of the country. The Alma-Ata Declaration was aimed at promoting equity and community participation through a focus on prevention and appropriate technologies and an integrated intersectoral approach to development. Health for All was regarded as a value system with primary health care as the strategic component.

The implementation of PHC required rethinking health systems’ organization and management, and redirecting policies, strategies, and resource allocation (financial, physical, and workforce), a task which faced a plethora of cultural and political barriers.

The focus on rural and on the most deprived urban population groups, on basic health services, and thus on the primary needs and pathologies of the poorest people, was met with resistance from the social hierarchy and power base in many countries. The economic, political and intellectual elite instead preferred to develop hospital health services that were highly specialized, costly, and therefore unsustainable. Doctors’ incomes, as well as their social and professional standing, was linked to their level of specialization and to technological sophistication, rather than to the value of the service they provide to patients. Indeed, in line with their training, health professionals have been historically more concerned about the clinical aspects of disease rather than about social determinants of health heavily influencing the medicalization of health systems. Ministries of Health had very little political weight for a host of reasons, not the least of which being that Ministries of Finance determined their budgets. Furthermore, even the countries that were more determined to introduce PHC had to face obstacles related to a lack of both financial and human resources, a plight affecting all developing countries (albeit to varying extents). The Alma-Ata Declaration was criticized for being too broad and idealistic and that the slogan “Health for All by 2000” was simply not feasible.

Only one year after Alma-Ata, a workshop entitled “Health and Population in Development” was hosted by the Rockefeller Foundation in Bellagio (Italy) and supported by the World Bank, with the Vice President of the

Ford Foundation, the administrator of USAID, and the Executive Secretary of UNICEF in attendance. The meeting engendered the “selective Primary Health Care” approach, which consisted of a series of interventions that were low-cost, pragmatic and limited in scope. Selective PHC significantly narrowed the original, innovative approach and concentrated instead on the application of selective measures that should be aimed at preventing and managing those few diseases that cause the greatest mortality and morbidity and for which there are medical interventions of relatively high efficacy. Following that revised approach, the design and organization of programs would soon follow a top-down dynamic, a stark contrast to the bottom-up model of PHC, which instead prescribed decision-making by the local communities. These measures were selected according to questionable cost-effectiveness criteria. Under the strong influence of international organizations and bilateral agencies, this soon resulted in the reorganization of health systems into vertical programs. The fragmentation of public health activities created a complete detachment between these programs and development programs in other sectors (schools, production, environment, etc.).

Vertical Programs dealt with specific diseases or interventions (diarrhea, malaria, tuberculosis, immunizations, etc.) and were formulated at the central level, then implemented throughout the country (or throughout the world) in a uniform manner, and often with rigidly assigned resources and independent planning and reporting procedures. Sometimes, separate institutions were even set up for each program.

This disease- rather than health-oriented approach was often more concordant with the political and administrative needs of main donor countries and organizations, who had a strong influence on the choices of beneficiary countries. The relatively cheap yet highly visible and publicized campaigns typical of the selective PHC approach, often served to mask the lack of political determination that was needed to overhaul the health system and improve overall health conditions.

This quite reductive, centralist approach was soon to become the dominant mind-set; attention was drawn away from health and health systems and focused instead on the control of single diseases.

As the selective PHC approach did not require significant investment in public health and system reorganization, it suited neoliberal macroeconomic policies that had started to take hold in the early 1980s.

The debt crisis of the 1980s played a critical role in launching the IMF and The World Bank (known as the Bretton Woods institutions) onto the global stage. The Bretton Woods institutions were called to contain DCs external debt crisis. In order to ensure that obligations to private creditors were fulfilled, poor, indebted countries were offered new access to credit however bound to the application of a standard set of macroeconomic measures known as Structural Adjustment Programs (SAP). The SAPs envisaged substantial cuts in the health, education, and other welfare spending; liberalizing imports; removing restrictions on foreign investment; privatizing state companies and financial deregulation; devaluing currency; cutting wages; and weakening labor protection mechanisms.

Adjustment policies had dramatic (and often debilitating) effects on large swaths of the population and severely weakened public health systems. In 1993 with its annual flagship report “Investing in Health”, the World Bank legitimated itself as a new leader in global health. The Bank put renewed emphasis on a “selective” approach by means of a “minimum essential package” for the control of a limited number of diseases and continued advocating the privatization of health services [3].

Yet, despite the policies imposed by the Bretton Woods Institutions, a number of experiences kept alive the spirit of Alma-Ata and the need for systemic and integrated approaches.

In 1986, the Ottawa Charter on health promotion introduced the concept of “healthy public policies” highlighting the unavoidable influence of policies outside the health sector and the need to put health on the agenda of policymakers in all sectors and at all levels [4]. The following year at the Harare Conference in 1987, decentralization was again raised as a means of applying PHC, with districts promoted as the best way of identifying the underserved populations and aligning appropriate health interventions.

After the decade of decay that followed Hafdan Mahler’s charismatic leadership, under Director General Gro Harlem Brundlandt, in 1998, the WHO adopted new strategic directions, with an extended focus on sustainable health systems linked to combating poverty, underdevelopment, and social inequalities.

The integration of health interventions in a wider inter-sectorial development and fight against poverty approach was also reaffirmed in the Reference Document on health initiatives in the context of fight against poverty jointly produced by WHO and OECD in 2003.

Nevertheless, in contrast with the broad outlook that WHO advocated, in practice Brundtland openly supported “vertical” initiatives through Global Public Private Partnerships (GPPPs) to face a variety of diseases and health issues, including the Stop TB initiative, Roll Back malaria, Malaria Medicine Initiative, International Partnership against AIDS in Africa (IPAA), International AIDS vaccine initiative (IAVI), and the Global Alliance on Vaccines and Immunizations (GAVI).

The HIV/AIDS epidemic brought back health on the global policy agenda, however conditions like malnutrition, diarrhea and acute respiratory illnesses, which attracted attention in the past and whose mortality rate was, and still is, very high, seemed to be forgotten; not to speak of the emerging burden of non-communicable diseases (NCDs).

Among the Millennium Development Goals (MDGs) identified after the Millennium Summit celebrated in 2000 in New York, health goals occupied an eminent position. Although the commitment to the attainment of the MDGs by 2015 was at the origin of a significant increase in global resources for Development Assistance in Health (DAH), unfortunately, the MDGs allowed the global attention and resources to be focused once again on selective approaches, especially regarding three diseases under MDG 6 (HIV/AIDS, Tuberculosis, Malaria). MDG 8 (Global partnership) supported the GPPP formula which had emerged between the end of the 1990s and the beginning of the new century. The model had gained special momentum through the launch of the GAVI established in 2000 with an initial funding of USD 750 million of the Bill & Melinda Gates Foundation.

The creation of the Global Fund to fight HIV/AIDS, Tuberculosis and Malaria (GFATM), built on GAVI's model, represented a paradigmatic case of political convenience prevailing over technical considerations. The initial proposal of the G8 Italian Presidency clearly envisaged an integrated approach to health; instead the following negotiations limited the scope of the future Global Fund to just three diseases.

GPPPs mushroomed. Only in the health sector the number of GPPPs rapidly increased to surpass 90 different types of initiatives and organizations, fragmenting action and governance for health at all levels and were evidently in contrast with the growing awareness about the need for strengthened health systems and wider health coverage for the most disadvantaged populations.

In 2008, on the 30th Anniversary of the Alma-Ata Declaration, the need for a more holistic and systemic approach was raised by the World Health Report "Primary Health Care now more than ever". The Report critically highlighted the factors interfering with health systems functions, i.e., focus on hospital care, fragmentation resulting from programs and projects' multiplication, and the pervasive commercialization of health care. In response, universal access and social protection should go hand in hand with health service reorganization around people's needs and expectations [5].

The same year the WHO Commission on social determinants of health emphasized the need to improve daily living conditions and tackle the inequitable distribution of power, money and resources [6]. At its 2008 Toyako summit also the G8 focused on strengthening health systems, and the following year at L'Aquila, eight years after the Genoa summit when the original systems approach had been deleted from the agenda and substituted with the launch of the Global Fund, the G8 promoted a comprehensive and integrated approach to the achievement of the health-related MDGs with health as an outcome of all policies. Finally, the World Health Assembly stressed that health improvement cannot be achieved by simply investing in specific health interventions, but requires an approach based on human rights and health as a fundamental right, as well as important economic and social changes.

Thus, over thirty years after Alma-Ata, the systemic approach seemed to regain priority in the global agenda. Universal access to care was emerging as an important policy objective linked to the right to health and to the debate on strengthening health systems. In 2010 the WHO World Health Report in 2010 was focused on "Universal Coverage".

As the MDGs' 2015 deadline drew closer, the limitations surrounding the MDGs and the strategies used to attain their targets came under scrutiny, and the debate intensified about the future development agenda. Unlike the process that led to the MDGs, the post-2015 development agenda was the result of a wide and rather inclusive process. The "2030 Agenda for Sustainable Development" adopted on the 25th of September 2015 by the United Nations Summit of the Heads of State and Government, committed governments to adopt a comprehensive, far-reaching and people-centered set of 17 universal and transformative "indivisible" Sustainable Development Goals (SDGs). The SDGs aim to put an end to poverty by 2030, combat inequalities, ensure lasting protection of the planet and its resources, and create the conditions for 'shared prosperity' and 'sustainable, inclusive and sustained' growth [7]. The progress toward the achievement of the SDGs in general, and of "healthy lives and well-being for all at all ages" (SDG3) with its targets and actions in particular, will be largely determined by the balance of forces involved and the vision that will prevail.

To "achieve universal health coverage" is but one of the targets of SDG3 (3.8), however it has become central to the debate on the achievement of the SDG. WHO describes UHC as "UHC means that all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation, and palliative care" [8].

Although UHC is also consistent with the concept of "Health for all" and the Alma Ata Declaration and can be regarded as an essential component of primary health, there has been a tendency to substitute it to Alma-Ata's "health for all" objective and "Primary health care" strategy, and to confound PHC with the primary level of care.

In the 40th anniversary of the Alma-Ata Declaration world's Ministries of Health and other stakeholder met in Astana where they renewed the commitment to PHC putting emphasis on UHC. The new declaration was criticized as a step back from the Alma-Ata commitment. Critics were concerned that the 2018 declaration framed PHC primarily as a foundation of UHC. "PHC, is broader and indeed subsumes UHC, which is, in many countries, being implemented by private health insurance companies and aggravating health inequities" [9]. In

the new declaration a new vision of PHC beyond the mainstream UHC rhetoric was missing. As Clarisse Etienne, Director of the Panamerican Health Organization (PAHO) straightly put it: “It is not merely the first level of care, nor is it the provision of a limited package of services for the poor. PHC calls for universal access to quality, comprehensive health services not only curative but: for promotion, prevention, rehabilitation, palliation and treatment of common conditions. It calls for addressing the social determinants of health. ... fragmentation and segmentation of health systems and services is a recipe for failure. ... Please, please, please - do not reduce health to merely the access to minimum sets of packages of essential services, when your peoples deserve so much more! ... We cannot leave here [*the Astana summit*] and repeat the mistakes of the past, in instigating reform processes that weaken governance and stewardship, that reduce primary health care to ‘minimum sets of poor services for the poor’ [10].

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Globalization and Health

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In the broadest sense, globalization has become widely understood as the closer integration or interconnectedness of human societies across geographical or political boundaries. While this has been the case for millennia, what is new in recent decades is the vast increase in the quantity and speed of transboundary flows, and their geographical reach.

Globalization is clearly enabled by technological advances which make flows across borders faster and cheaper, and hence much more pervasive. For example, the decline in freight cost per ton by sea and air freight has promoted the rapid growth of international trade as well as the large-scale shift of manufacturing activities to low-cost countries. Not surprisingly, information and communication technologies have also been frequently cited as the major force behind globalization.

For some writers, however, technology is an enabler, but not the driver, of globalization. They argue that the real factors driving technological developments and their application are economic in nature. The global spread of capitalism has been spurred, on the one hand, by untold thousands of producers seeking access to cheaper inputs (i.e. raw materials, labour, research and development, transport and communications), most efficient (and greatest) economies of scale, and largest potential markets. Billions of consumers around the world, on the other hand, fuel this process by demanding the highest quality and quantity of goods and services at the lowest possible price. The economic transactions that result, what eighteenth-century economist Adam Smith called the ‘invisible hand’ of the market, are seen as the real force behind globalization.

A further perspective rejects globalization as an essentially technological or economically driven process which implies a degree of rationality and progress. Instead, current forms of globalization are seen as driven by particular ideologically based values and beliefs broadly referred to as neo-liberalism. It has been the global spread and dominance of this ideology from the 1980s, and its embedding within global institutional arrangements, that has, for instance, defined the industrial policies facilitating the development of such technologies (e.g. the promotion of an information economy through deregulation and privatization of the telecommunications sector), and their dissemination for particular purposes (e.g. deregulation of financial markets). It is argued that neo-liberalism has also defined economic policies which encourage trade liberalization, market-based competition, and foreign investment (e.g. tax incentives), while advocating a minimal role for the state at the expense of social welfare and environmental protections. The global financial crisis from 2007 has led to a rethinking of neo-liberalism and calls for stronger global regulation.

From a public health perspective, there is strong evidence that globalization is leading to diverse and complex changes to health determinants, as the case of food industry shows.

The globalization of the food industry has raised widespread public health concerns about the rise in non-communicable diseases (NCDs) worldwide. Changing dietary patterns are one of multiple factors, notably physical inactivity, tobacco and alcohol use, and built environments, that must be better understood. The increased production and consumption of processed foods, for example, has increased salt intake and consequently hypertension among populations worldwide. The stark rise in adult and childhood obesity has been attributed to the availability and affordability of ‘energy dense’ foods (high fat and sugar). Lang et al. assessed compliance by 25 of the world’s largest food manufacturers and retailers to recommendations concerning ingredients, advertising, portion size, and labelling [1]. Only a small proportion of companies are voluntarily reducing salt, sugar, and fats in their products. While the public health community has pushed for stronger regulation, governments to date have favoured industry initiatives such as voluntary codes. The 2004 WHO Global Strategy on Diet, Physical Activity and Health was also given no regulatory ‘teeth’ by member states, and the political declaration of the 2011 UN High Level Meeting on Non-Communicable Disease Prevention and Control has failed to generate the sustained popular attention and donor resources [2].

Neo-liberalism has also strongly influenced global health policies, as Whitehead, Dahlgren and Evans write on the Lancet: “In the past two decades, powerful international trends in market-oriented health-sector reforms have been sweeping around the world, generally spreading from the northern to the southern, and from the

western to the eastern hemispheres. Global blueprints have been advocated by agencies such as the World Bank to promote privatisation of health-service providers, and to increase private financing-via user fees-of public providers. Furthermore, commercial interests are increasingly promoted by the World Trade Organisation, which has striven to open up public services to foreign investors and markets. This policy could pave the way for public funding of private operators in health and education sectors, especially in wealthy, industrial countries in the northern hemisphere.

Although such attempts to undermine public services pose an obvious threat to equity in the well established social-welfare systems of Europe and Canada, other developments pose more immediate threats to the fragile systems in middle-income and low-income countries. Two of these trends-the introduction of user fees for public services, and the growth of out-of-pocket expenses for private services-can, if combined, constitute a major poverty trap” [3]

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Anthropological aspects of health

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Thomas H. Eriksen, defines anthropology as a discipline that “*has the whole of human society as its field of interest, and tries to understand the connections between the various aspects of our existence*” [1]. In this sense, it is self-evident that health cannot but represent one of the points of interest of the discipline. Medical anthropology is in fact an important branch of anthropology as a whole, but, as it will be discussed in this brief chapter, the relationships between anthropology and health do not coincide precisely with the studies carried out by medical anthropologists alone.

Medical anthropology represents a traditional field of investigation for academic anthropologists, whose target is the description of specific healing or ritual practices, belief systems and habits connected to health with the aim of giving them a theoretical interpretation, often without considering possible applicative outputs for their researches.

Indeed, considering the definition of health given by the WHO in 1948 which sees health as “*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*”, it is clear that health is, by its very nature, an omni-comprehensive, complex domain.

On the basis of this definition, the Western world has developed two specific branches for medicine: public health and, more recently, global health, whose objective is to focus not only on the bio-medical factors impacting on people's lives, but also on all other environmental elements which contribute, as inputs, to context-specific outputs in terms of health on different people, communities or groups. These external elements have been defined as the social determinants of health. When health is considered in this perspective, its interconnections with anthropology multiply with a snowball effect.

Although until now anthropologists seem not to have identified with global health a specific field of investigation, some interesting work has been done in this direction [2, 3, 4, 5]. One of the main issues in the current debate on the role of anthropology in public or global health is its applicability. If, in fact, the role of anthropologists as theoretical critics is largely accepted in the academic debate, their role as applied scientists is still not accepted by a large number of colleagues, who see applied roles as “*fraught with ethical, methodological and political problems*” [6]. Anyway, conscious of this diffidence towards their work, nowadays more and more colleagues take the ethical choice of becoming involved in applied fields in order to do their part in trying to limit the impact of globalization above all on vulnerable, minority groups, both in the marginalized fringes of the richer and technologically advanced Western societies and among the indigenous or rural peoples living in developing countries.

Anthropology intersects global health in a number of sub-domains which represent the key arenas of research and practice and which range from the study of:

- a) traditional healing and belief systems;
- b) context-specific perceptions of what health is and means [7];
- c) the impact of specific public health plans and international health programs on the local population [4, 8];
- d) the production, circulation, use and abuse of medical substances [9];
- e) mental disorders, their origins, views and treatments [10];
- f) the social stigma bound to specific diseases [10].

In this perspective, it is obvious that the floor is open not only to (traditional) medical anthropologists, but also to those of us who have different interests and specializations, as for example, experts of development studies, of social and gender issues, of linguistics, of risk perception, of religion, of social and environmental changes. The list could be extended *ad libitum*.

Starting from scratch, our work takes its origin in the same basic assumption, i.e. the definition of sickness, disease and illness given some 40 years ago by medical doctor Marshall Marinker [11]. According to Prof. Marinker:

“*Disease [...] is a pathological process [...]. The quality which identifies disease is some deviation from a biological norm. There is an objectivity about disease which doctors are able to see, touch, measure, smell.*”

Diseases are valued as the central facts in the medical view [...].

Illness [...] is a feeling, an experience of un-health which is entirely personal, interior to the person of the patient. Often it accompanies disease, but the disease may be undeclared [...]. Sometimes illness exists where no disease can be found. Traditional medical education has made the deafening silence of illness-in-the-absence-of-disease unbearable to the clinician [...].

Sickness [...] is the external and public mode of un-health. Sickness is a social role, a status, a negotiated position in the world, a bargain struck between the person henceforward called 'sick', and a society which is prepared to recognize and sustain him.

The security of this role depends on a number of factors, not least the possession of that much treasured gift, the disease. Sickness based on illness alone is a most uncertain status [...].

This three labels indicate the three dimensions in which anthropologists shall investigate in order to be able to offer a complete context-specific analysis of any case studies: the *intimate* one, sometimes impossible to share; the *objective* one, referred to a consolidated medical taxonomy (no matter if bio-medical or popular); the *public* one, sometimes characterized only by social stigmatization of bodily conditions (the albinos in Tanzania), personal orientations (the homosexuals according to some part of the Catholic Church) or *habitus* (the pervasive idea of a cause-effect bond between the use of heroine and HIV/AIDS in urban peripheries).

Considering these three dimensions means to act at the same time on three different stages and, even though the same drama is presented on the three of them, the way in which it is played and interpreted can be very different. Therefore, the anthropologist's task should be to harmonize the three narratives in order to offer a picture as complete as possible of the whole scene.

If this task is already quite complex when the object of the study is a context to which both the researcher and the reader, or the public health workers are familiar, things become more and more complex when under the researchers' lenses a totally different culture is placed.

When facing indigenous, mostly illiterate, rural societies in Africa, South East Asia, the Eastern Pacific, Central and South America, or even very small indigenous enclaves of the Western world (think for example at many native Americans, or at some Finnish Sami tribes), researchers should be conscious that in those contexts there is a totally different perception of health.

Ideas of health or un-health are, indeed, traditionally based on a totally different conceptualization of the body-soul relationship and between the natural and the supernatural world [5].

In most illiterate societies a scientific, illuminist approach to life and death is not the rule and the logic on which people base their ideas, beliefs and practices is rooted in a magic-religious world in which un-health is seen as the rupture of a cosmic equilibrium.

This means that, according to this logic, people can be affected by an illness, disease or sickness, if a) they have done something contrary to their tradition (e.g. they did not respect their ancestors, their deities, their kin or their neighbors); b) they have been objects of sorcery or witchcraft; c) they have been punished for not having respected sacred places, objects or people [7].

According to this logic, all the illnesses, diseases or sicknesses that a person experiences through her life can be symptoms of the same supernatural infraction and people are frequently convinced that they cannot really recover from their un-healthy condition, if they do not receive, together with a specific medical remedy (be it traditional, herbal or "modern", chemical), a ritual treatment aimed at the purification of their souls.

In a globalized world, of course, Western medicine is by now available even in the most remote areas of the globe, and the same is true for many other alternative medicines (Chinese clinics above all are, for example, pervasively present in Africa) thanks both to the implementation of a more widespread coverage public health plan even in vulnerable countries and to the job of many charities or NGOs active on the field, and people refer to it as much as they can¹.

Nevertheless, because of their ancestral *forma mentis*, usually they think of these "modern" techniques as representing only the quickest way to reach a hopefully immediate disappearance of the physical symptoms. A disappearance which they need to make durable undergoing a mystical treatment.

The consequences of this attitude are many and sometimes very risky. On the one hand, illiterate people are usually not aware of the risks connected with the misuse or to the abuse of medical drugs, and, still worse, of the risks connected with the contemporary assumption of different kinds of remedies. Many times they just think that taking together traditional herbal remedies and western drugs cannot but result in a better and quickest solution to their bodily problems.

On the other hand, in those cultures where the conceptualization of health/un-health is rooted in a cosmo-vision which sees illness as the symptom of a broken equilibrium, it is evident that categories such as prevention, contagion and chronicity could be hard for the people to understand.

In conclusion, given the depth and complexity of the health domain and of the various impact factors and overlapping issues connected with it, the role of anthropology, besides offering accurate analysis of the context

¹It is not the case here to consider all the factors that usually prevent indigenous, poor people to have access to modern medicine and health centers. Suffice it to mention here the often too long distance between villages and hospitals, the high costs of the treatments and the uncaring behavior of many nurses and doctors employed in the public health posts.

specific cultural views and values, should be to help health workers to understand them and to find the right way to mediate and communicate with all the social groups involved, trying to find creative solutions, maybe starting from what, in the local, traditional practices can be valued as good, even if new knowledge and techniques must be proposed and adopted.

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United Nations system and other International Organizations action in International and Global Health: achievements and challenges. A view based on personal experience

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INTRODUCTION

The vision what happened in our world is interlinked, at natural and individual level, emerged in Europe in the middle of the 18th century and was clearly stated in the 19th century by Alexander von Humboldt [1]. The approach to this fact, initially linked to the romantic movement, has been variable since then and is influenced by ideology, economy, science and, of course, politics. The present framework includes the fact that after the second world there is a functional United Nations (UN) system and in the last two decades growing and stronger influence of bilateral cooperation of industrialized countries and international NGO.

Recently there has been a debate about the use of the terms International and Global health. The present trend is to use Global health, which, according to some opinions, considers “one” global population, which should be treated in a supra-national way and the global activities of non-governmental organizations [2]. This is not evidence based and may be related to academic supra-national research issues, national bilateral interests and implementation of international NGOS projects. Issues related to global governance are closely related and include attempts to re-discuss of the UN role.

For this paper both global health and international health will be used as the author considers that is better to discuss historic and present attitudes of persons and governments and content of interventions, rather than engaging in terminology discussions, not free from biased personal and national interests. The author believes that health issues are global and a supranational approach, respecting human rights and rights to self-determination, is not only needed but the only way to improve health of the global populations.

The discussion will cover some key historical aspects and the author's experience working with The World Health Organization (WHO) from 1978 to present, being a staff member from 1994 to 2013.

The dialogue of the past with the present

The first global peoples movement occurred in relation to the European travel to the American region beginning in the 15th century. It is true that before, relations between Asia, Africa and Europe occurred. Epidemics travelled with ships and caravans from east to west and from west to east as well as medical practices (e.g. Islamic medicine influence in Salerno and Montpellier medical schools). The 15th and 16th century's commercial exchanges were accompanied by new epidemics in both sides of the Atlantic Ocean. Smallpox and other diseases from Europe decimated natives in the Americas. Syphilis travelled west to east to Europe and then further east to reach Japan. Plague, as before, moved from Far East to west. Malaria and Yellow fever were transported from Africa to the Americas [3]. Together with diseases movement started also effective (e.g. quinine for malaria) and ineffective (e.g. guaiacum for syphilis) medicines travelling from Americas to Europe. Ships and colonization companies were equipped with medical officers and ports were surveyed to protect individuals and populations. Globalization had started and with it Global health. Health and diseases movement became a concern for countries, colonization companies and institutions providing care, such as the missionaries of the catholic and reformat churches. At this stage we can already identify the main sources to today's approach to global health: nations political and commercial interest, multination's agreements, knowledge development, the project approach of the missionaries, the individual willingness to help the others.

The relation of commerce with disease control was, and still is, a continuous concern. Carlo Cippolla, for instance, describes very well the plague control measures in 17th century Italy. Based in detailed original documents found in Prato and Florence, Tuscany, Italy, the dynamics, and conflict of public health measures and commerce in described [4].

The first attempt to mediate and regulate international conflicts in health was the establishment Egyptian Sanitary, Maritime and Quarantine Council in 1831. This was followed in 1851 by the First International Sanitary Conference (Paris), which was an attempt from 12 countries to protect Europe from cholera and to facilitate international trade. In 1892 it was established a limited agreement to impose quarantine on ships carrying cases of cholera on board. In 1907 the Office International d'Hygiène Publique (OIHP), was established in Paris, which it is somehow the predecessor of the League of Nations Health Organization's health office in the 1920's and the World Health Organization, established in 1948.

All these events encompass regionals or a global multi-nations approach to global health. Contemporary version of this focus is the UN system, with multiple agencies involved in health (e.g. WHO, UNICEF, UNFPA, regional institutions as European Union and African Union), and international health funds sponsored by groups of industrialized countries (e.g. The Global Fund Against Tuberculosis, Malaria and AIDS).

In parallel of this developments countries with colonial interest had, during 19th and early 20th century, a "colonial medicine" approach based on colonial science and finance. The main objective was to keep the coloniser's health, mainly in urban areas, with few efforts to incorporate local perspectives or participation. This has evolved to training basically limited to lower levels of health services. Rural medicine was left to missionaries with focus in maternal and child health. Diseases specific approach of this period included Boubas and Syphilis control in East Africa, campaigns against schistosomiasis in Egypt and China, measures against plague in India and campaigns against cholera in the Philippines [5]. At this period American institutions such as Rockefeller Foundation and Institut Pasteur came to the international stage and the first public health schools were established. Contemporary versions of these approaches are the national bilateral cooperation agencies (GTZ, USAID, Swiss Cooperation, SIDA, etc...), International activities of Universities, Global Health foundations.

Many are the tensions in global health. Focus in prevention or in care, priority to individual or population's health, emphasis in specific diseases elimination and eradication or in health systems development? All these elements influenced by the investment and interest of industrialized countries, the main donors, and middle and low income economies internal priorities and politics

International health also moves, in the past and in the present, with different ideology backgrounds. Should International health be linked or separated from development? Should specific action wait for health systems development? What should be the way health is financed?

International Health Today

Today the world is only one. Certainly with nations, but with such a high populations and merchandises movement that political and personal attempt to revert the situation has a high probability of failure. Therefore more than ever health of individuals and nations in one place influence easily other places, individuals and nations. Many are the actors in public health and there is no agreement with the best approach to tackle it.

One of the factors present today is the danger of global epidemics. It is a recurrent, and possible issue, which, for variety of factors is difficult to be materialized. The HIV epidemic, which started at global level in the early 80's, is an example. With an African origin found conditions of vulnerability all over the world. Other menaces, e.g. as Asian flu, Ebola, were contained at sub-regional level. These factors led to an expanded role of multilateral organizations such as the World Health Organization, which, in response, strengthen global surveillance [6] and international health regulations [7]. On the other hand these potential menaces had increase industrialized countries prevention and care aid activities and reinforced a control at borders

Action of global actors in global health depends main on the strength of their economies, national/institutional culture, history, tradition and politics (which is the main changing factor in nations)

Bilateral aid agencies (e.g. GTZ, USAID, SIDA, etc.) are linked to governments and usually prefer to work with countries with which have commercial and/or strategic interests. Language and previous relations as colonial power play an important role. United States of America have, for instance, has an important bilateral multi country programme, PEPFAR [8], the "United States President's emergency plan for AIDS relief", which has survived four presidential mandate and is a major source fund for HIV/AIDS care in low-income economies. The problem of sustainability when funds decrease remains unresolved.

Horizontal cooperation has been a constant willingness but remains mostly a wish than a reality.

Foundations, such as Bill and Melinda GATES foundation [9], are also major players in Global Health. Sometimes they priorities are decided with limited consultation to recipients' countries and their project approach, good to show results, is not the ideal to promote development of health systems and outcomes in the broad sense of the term. To compensate this fact they also provide significant funds to UN system agencies.

There are many UN systems agencies related to promote health, being the World Health Organization the main one. Others include UNFPA, UNESCO, UNICEF, UNDP, just to quote a few. UNAIDS is a multiagency programme composed by 10 UN agencies. WHO is the only one with a comprehensive approach and with more than 180 member countries it has a global presence at regional and country level. Presently, it has the trend to

concentrate in few health issues, under the umbrella of universal health coverage. Also WHO presence at country level should be increased. WHO present priorities are: promote health, keep the world safe and save the vulnerable [10]. It is an interesting mix, which includes prevention, care, control of global epidemics and priority of the underserved. It could be said it is a synthesis of different approaches to global health. The UN system has the advantage to work in global health with all countries having the same status. Nevertheless its financing is mainly ensured by industrialized countries (regular and extra budget).

In the beginning of the 21st century, as an initiative of a group of industrialized countries (G8) The Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) [11] was established. It is today the main source of international funding for these three diseases.

Academia is also heavily involved in Global Health. Universities are more and more developing agreements and mobility in education and research. Mobility of students and researches contribute to accelerate research but also has the, not negligible, deleterious effect of brain drain from low and mid income economies to the industrialized ones.

Many are the background and motivations of individuals working in global health. Certainly is a multidisciplinary field evolving potentially almost all professions. Of course the health sector is the one attracting more people

Willingness to travel and to know different people and places is a key factor. Also, sometimes, it is related to a specific technical area, such infectious diseases or international relations.

Ideology and politics also play a role in the choice of being involved with the health of people living in low-income economies and in poor conditions. Caring for the others has been always a drive to work in health. Missionary approaches, which started centuries ago, continue to play an important role.

The fact is that, in the present status of global formal and informal networks the world is definitively linked. Health just follows the pattern of this entire system of connections. Countries and institutions should take this into consideration in their health and cooperation strategies.

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Impact of migration on global health issues

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Who is a migrant? *An individual who has resided in a foreign country for more than one year irrespective of the causes-(voluntary or involuntary) and the means- (regular or irregular) used to migrate* [1]. There is no universally accepted definition for migrant.

Human beings have always been migrants. Their natural instinct and ambition have historically driven them to look for better conditions. Economical opportunities, study & health access, security, environmental changes, religious or sexual persecution or simply the right & need to explore have always pushed individuals to flee.

Unfortunately migration has recently become the protagonist of communication: very rarely media do not cite migration events in their daily news.

As a matter of fact, particularly in the last decade, migration has given the opportunity to reshape the socio-political snapshot of the world: a mix of misconceptions, fears, ideals and truths is shaken into a complex “communication cocktail”.

For this reason it is essential to start from real figures.

How many migrants are there in the world? Is there “one type” of migrant?

This is the first challenge. Migration is a dynamic and unstable process by definition. Tracing migrant numbers requires huge economical, legal and political efforts.

Different means (research, active and passive census, international institutions, NGOs and States..) contribute to reach reliable figures. There are currently two main international datasets on international migration flows, both of which are derived from national statistics: UN DESA’s International Migration Flows dataset and OECD’s International Migration Database [2].

By mid-2019, 271.6 million of migrants have been estimated as 3.5% of the total world population (7.5 billion) However these figures do not take into account internal migration, which is even higher. About 740 million people have moved within their own country according the most recent estimates. Migration dynamics have changed: reduction in travel costs and spread of digital communication have certainly shortened cultural and physical distances in-between populations.

On the other side, inequality, poverty, political instability and, last but not least, climate change have not reduced over the time, pushing people to escape from an unfavorable destiny. The trend is in permanent increase: the estimated number of international migrants doubled in 1990 (153 million) and has now reached over three times (271.6 million), both compared to the 84 million registered in 1970. One every 30 people is a migrant; 72 % of working age (20-64 years), 52% males and 48% females. In 2013 112.3 million of migrants workers (2/3 of the total migrant population) resided in high income countries whereas 34.2 million were living in low-middle income countries according to ILO 2015 dataset. Most of migrants are economical ones (workers and students); family reunion comes as a natural consequence whereas a small percentage is represented by tourists. Nevertheless, the most *popular* category of migrants is covered by asylum seekers and refugees even though they still represent a minority of the total ones. If we consider migration from the legislative point of view we can divide migrants into documented and undocumented ones. This variable is pivotal in first and mid-term migrant life, having fundamental consequences on health. Let us now focus on migration health. Firstly we need to move from the old photo of “male, strong, selected, healthy migrant” to a set of different photos. In fact minors and female have become more and more present as old or sick people do not represent an exception anymore. Migrant health is not synonymous with infectious diseases and encompasses different medical topics. Post traumatic diseases (burns, casualties, sexual violence, post traumatic stress disorders), as non communicable morbidities (obesity, diabetes, hypertension,) are amongst the commonest reason of access to health facilities. Migrant health on the one hand reflects epidemiological group characteristics (f.e. increased cardiovascular risk among specific groups [3], MDR TB from eastern Europe, PTSD from conflict areas); on the other hand has been influenced by globalization (sedentary style of life, exposure to pollution, tobacco, alcohol, diet modification) [4].

According to migration, determinants of health can be divided into pre-travel, travel return and host-community determinants of health [5].

Amongst the first ones, we cannot but take into consideration the country of origin. How is the health system organized in Pakistan versus in Gambia? Which are the most prevalent diseases in Syria or in Philippines? How the population is composed in Somalia? How the national vaccination program is actually implemented in Bangladesh? The health system is functioning or has been hampered by political decline, post-war reconstruction? These are only some of the elements that we should analyze before depicting health migrant profiles.

Travel determinants namely consider the travel route (length, crossed countries, crossed epidemics, detention, accidents and violence occurred, condition of life in the transitory countries).

Analyzing sub-Saharan migration, thoughts immediately run to Libya where repeated imprisonment and sexual harassment are strictly related to the development of infectious diseases (TB, HIV and STIs, scabies, chronic and acute gastroenteritis...) and non communicable diseases (in primis psychological disorders and morbidities such as depression, PTSD) [6].

Malnutrition often dominates travel history: very limited quantity of food and safe water were reported during sub-Saharan travel route.

When examining, migrants at arrival, the effects of travel might be dominant [7] but the picture will change if we meet them some months later.

This is particularly true if we consider post-stress disorders which may appear 6 months after arrival, if not later on.

At arrival, migrants have to adapt to a whole new world (language, habits, food, shelter, people..) and consequently travel traumas (loss of family members and friends, violence, forced imprisonment) may be initially removed or simply “put aside” [8].

Moreover, arrival does not always imply immediate changes of living conditions: overcrowding, scarcity of ventilation, difficult access to basic hygiene and health services may persist for months and therefore contribute to the spread and reactivation of communicable diseases [9].

Post-arrival determinants of health will consequently depend on host-countries and condition of life.

It is well known that reception centers differ one each other for their dimension and quality. Some centers can put in place health, social and scholar services whereas others ones can just guarantee minimum standard of basic shelter and food.

Migrants at arrival can also not adhere to the standard system for asylum seekers and live in even more difficult conditions, often homeless or residing in occupied buildings. This phenomenon is well known and is gradually increasing in Italy as mentioned in the XXVII Immigration Report Caritas and Migrantes 2017-2018 (RICM): a new language for Migration.

Each European and world country has now experienced migration effects for decades in different ways. The effects of migration have been interestingly studied in the 2010 World Migration Report which particularly analyzed the influence of migration on urbanization.

The concept of “mega-city” is introduced as new cities where informal settlements grow side by side mixed neighborhoods. In this report migration is not only considered for its potential threats and difficulties (inequality, segregation) but also for its opportunities. The “Superdiversity” is described as new job profiles and experimental mixed social system (f.e cohabitation among native students and foreign ones, mixed marriage and new generations are analyzed as part of the scenario) with implications on the more extended concept of psycho-social health.

As a consequence, media should not be only overcrowded by security aspects, improper epidemics alerts, social intolerance but also inputs, discoveries and constructive experiences derived from exchange and intercultural dialogue.

Each country has faced migration effects on health systems differently and certainly there is no simple and unique solution for it. Several and various health policies and practices have been adopted in Europe with big discrepancies in terms of vaccination and screening procedures. In this sense ECDC and WHO have invested a lot in order to provide official guidelines and support to European countries [10].

In this panorama, Italian asylum seekers and refugees reception system was considered as a model until 2018 internal political changes. Despite the enormous difficulties to organize and implement dedicated services for the increasing flux of migrants through the years, a virtuous system was put in place (hubs, hotspots, extraordinary reception centers were functioning aside the more complex and developed “SPRAR”, Protection System for Asylum Seekers and Refugees). The 2018 Safety Decree certainly influenced the quality of assistance guaranteed in the previous years.

Luckily, aside a strong national health system, Italy can count on NGOs, religious and private association support to face the migrant challenge. The FAMI, (Fund for Asylum, Migration and Integration 2014-2020), co-funded by the Italian Interior Ministry and the European Union, has invested money in several psycho-social-health projects in the last decade.

One of this projects ("The Start Project": hosting transversal social-health services for Asylum Seekers and International Protection beneficiaries), saw the General Hospital of Brescia (ASST Spedali Civili) as main investigator and focused on the comparison of different health models. Two different settings, Milan and Brescia, both characterized by high migration pressure, and two different strategies were compared. Permanent health facilities activities in Milan were compared to activities performed by a mobile clinic in Brescia. Both models counted on a multi-disciplinary staff composed by nurses, medical doctors, psychologists, psychiatrics, health promoters, social assistants and cultural mediators. The project's results showed that a multidisciplinary mobile clinic was more rapid and efficacious in implementing screening activities for asylum seekers and refugees in Brescia. Compared to the past, where the National Health system provided health care in its permanent health facilities, the timing of access to the first medical evaluation was reduced by 60,7%, starting from an average of 8,9 days to 3,5 days. A prompt screening also favored a quicker access to diagnosis, treatment and care. New dedicated permanent services in Milan were less efficient in terms of timing but could develop highly qualified specialized services. Both approaches were built in collaboration with the national health system, having as a priority the reinforcement of the already existing network for asylum seekers and refugees. A mixed model of reinforcement of permanent national services and mobile activities, both based on multidisciplinary staff, had been strongly advocated as a major result of the project itself. This project recalls one of the challenges derived by migration: the linguistic and cultural barrier. As a matter of fact a multidisciplinary staff is essential to approach complex situations (post-traumatic disorders, undesired pregnancies, sexual violence are only some of possible examples) or simply to listen and properly take care of migrants. In this sense, the role of cultural mediators becomes pivotal in the dialogue in-between the migrant beneficiary and psycho-social-health staff. Mistakes may occur if this process does not take place: comprehension of chronic treatment and care; nutritional counseling, major health decisions, prevention cannot be implemented without. If during the emergency phase dedicated services may be necessary, inclusion in existing national services should be pursued in the long-term. Migrants cannot be simplified into a single category. Specific needs (epidemiological, social, cultural ones) according to each group of migrants should be faced by a holistic trans-cultural approach. In this sense, education represents one of the most important and cost-effective tool. Education to all the categories of health staff, starting from health assistants to highly specialized staff, must be regularly offered considering a multi-sectoral education. Legislative, public health, infectious diseases and tropical medicine, internal medicine and nutrition, maternal and health care, psychology and psychiatric, trans-cultural medicine, linguistic, social sciences are some of the topics that need to be constantly refreshed. Information, education and communication (IEC) must be a permanent package for health and non health staff but above all for beneficiaries. Newly arrived migrants and migrants at higher risk need to be efficaciously educated on health systems, access, prevention and investment on health. Education on vaccination, screening of preventable diseases, job, domestic, sexual, maternal & child health have to become essential part of the integration process. Education must be tailored according to the different phases of migration with appropriate tools: social media, visual and multilingual messages, cultural mediation, involvement of religious representatives, peer leaders and schools have to be part of the IEC package. Healthy communities are the result of good public health policies which consider local and newly arrived persons as a unique circle. Local people depend on migrants and vice-versa. This is essential for outbreaks control as for psycho-social community well-being. Global Health will not be pursued if migrant health is underestimated.

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Health Management in International Cooperation

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Global health is a fundamental human right but also a state of bio-psycho-social well-being, which does not depend only on the health system but also on the incidence that health determinants have on global inequalities: gender, level of education, income, employment, work and living environment, stigma, quality of social and health services....

Starting from data and indicators provided by the international organizations working in the sector of human development and global health, the civil society organizations (CSOs) [1] [2], operating in the field of international social-health cooperation are called to develop strategies, formulate programs and implement results-oriented projects that contribute to the achievement of the Sustainable Development Goals (SDGs), defined by the United Nations in 2015 with the launch of the 2030 Agenda for the sustainable development.

The main objective is aligned with the SDG n° 3 ("Ensure healthy lives and promote well-being for all ages") and other SDGs, such as: goal 1 "End poverty in all its forms everywhere", goal 2 "End hunger, achieve food security and improved nutrition and promote sustainable agriculture", goal 3 "Achieve gender equality and empower all women and girls", goal 6 "Ensure availability and sustainable management of water and sanitation for all".

The need assessments and the planning made by CSOs refer to different sources, which collect statistical data and indicators to describe the country, the local context, elaborate the need analysis and justify the project proposal. Among these, particularly important is the data provided by the annual Human Development Report of the United Nations Development Programme (UNDP) [3] and by the World Health Organization (WHO) [4].

The areas of intervention of the CSOs health cooperation projects are generally:

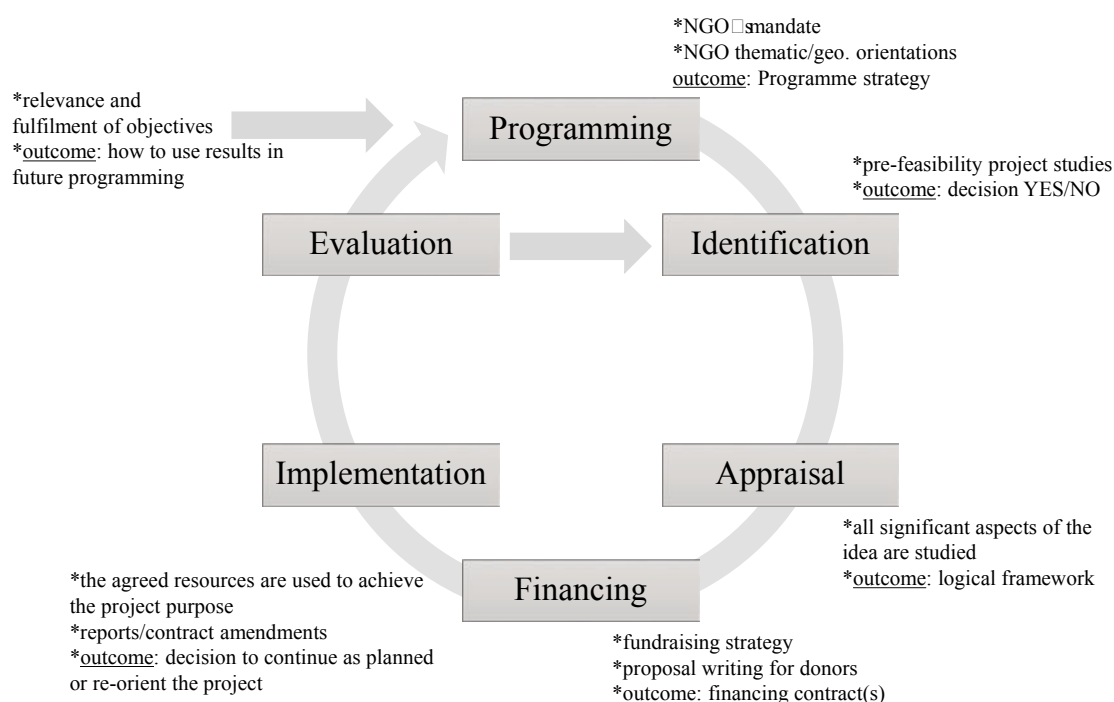
a) specifically healthcare (primary health care): maternal and child health, family planning, malnutrition, vaccination, diagnosis and treatment of the main infectious and tropical diseases, essential drugs, health education and health promotion; projects to strengthen local health systems (staff, training, infrastructure, information system, logistics);

b) socio-sanitary and economic development projects: water & sanitation, child protection, gender inequalities, food security, microcredit, etc;

But what does it mean to design, plan, write and implement an international cooperation health project? It means asking yourself key questions: "why?" (data and information on problems, needs and priorities of the intervention context - need assessment); "To whom?" (target group); "With whom?" (partnerships and stakeholders); "What to do?" (activities, results, indicators); "With what resources?" (human resources, service supplies..); "What are the possible risks?" (which require plans and prevention measures to be provided).

The main methodology for planning and managing international cooperation projects at European level is, since 2004, the "Project Cycle Management" (PCM) (Tab. 1), which uses the Logical Framework as the main matrix for planning, management, monitoring and evaluation of projects [5].

The matrix of the Logical Framework should be the result of an analysis process that involves the key actors of the project intervention, identifies the various problems and formulates them as existing negative situations ("Tree of Problems") and finally the reformulation of the problem analysis in positive situations you plan for the future ("Tree of Goals"). Following the definition of the goals of the action, the Logical Framework matrix defines the logic of the project intervention, which will indicate the sequential connections between the various elements of the project, in adherence with the need assessment and analysis of the problems, and with the planned responses through the involvement of key stakeholders.

Table 1- Logframe e project cycle

The latest version of the Logical Framework prepared by the European Commission-EuropeAid in 2016, discloses the trend towards a greater attention to the achievement of concrete, sustainable and socially accountable project results.

During the design phase of a project, the definition of the indicators and the relative sources of verification is considered increasingly relevant for the qualitative and quantitative evaluation of the achievement of the expected results and, therefore, of the specific objectives of the project.

Following this purpose the indicators must be "SMART":

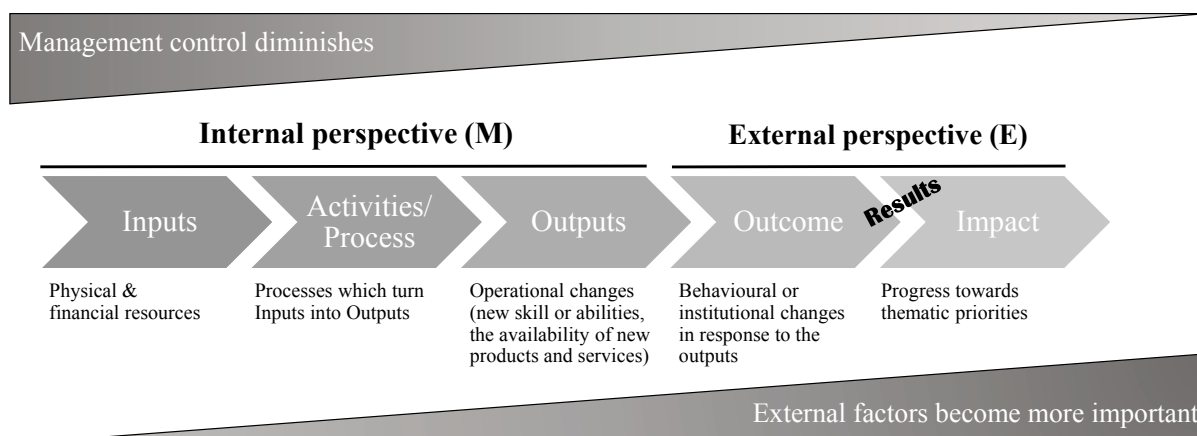
- Specific (for the objective to be measured)
- Measurable (quantitatively and qualitatively)
- Available-achievable (at acceptable or proportionate costs)
- Relevant (with respect to the need for information)
- Time-bound (expected time to reach the targets)

Over the years, the objective evaluation of the results achieved by the project, the impact and the change generated on the beneficiaries and in the area of intervention, has become increasingly important.

The progressive criticism of the "static" nature of the "PCM" model, focused on the "final product" (activities, expected results, objectives) led to the introduction of the "Theory of change" [6], a more flexible, rigorous and participatory approach (involvement of all stakeholders), which focuses more attention on the "process" and the sense of change. The "theory of change", according to the "chain of results", (Tab. 2) includes a logic of intervention oriented to the long-term objectives (impact) and to identify the conditions which must occur in order to reach the projects achievement [7].

The planning and management of international cooperation / humanitarian aid interventions, must include an absolute importance to the evaluation of the future sustainability of any project proposal, under different aspects: institutional, economic, environmental and socio-cultural sustainability. Once the project is finished, it is necessary to analyze and forecast in detail how the action can be economically sustainable, how it can be managed in continuity and autonomy by the local partners, and if the activities of any intervention do not harm groups or other vulnerable people.

Table 2- The results chain



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Health in epidemics, conflicts, and natural disasters

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The International Conference on Primary Health Care, held in Alma-Ata, USSR, on September 1978 express for the first time that health, “*which is a state of complete physical, mental and social wellbeing, and not merely the absence of disease or infirmity, is a fundamental human right* and that the attainment of the highest possible level of health is a most important world-wide social goal whose realization requires the action of many other social and economic sectors in addition to the health sector”.

Today, after more than 40 years, we are far away from achieving this primary objective, and this despite the objectives of the millennium goals, the fifteen-year period of development inaugurated by the United Nations in the year 2000 and ended in 2015. In fact, in the Millennium Summit held on September 2000, the General Assembly adopted the eight Millennium Development Goals (MDG) through the Millennium Declaration.

The General Assembly committed itself to reach the ambitious targets: eradicate extreme poverty and hunger, making primary education universal, promoting gender equality and women's autonomy, reduce child and maternal mortality, fight HIVD/AIDS, malaria and other diseases, guaranteeing environmental sustainability, develop a global partnership for development.

As the MDGs era come to a conclusion, without having achieved or having only partially achieved, the objectives, the United Nations launch “the seventeen Sustainable Development Goals (SDGs) as a shared vision of humanity and a social contract between the world’s leaders and the people.

Médecins Sans Frontières (MSF) was officially born on December 22, 1971 with 300 volunteers, including 13 doctors and founding journalists. MSF owes his birth to the fact that some French doctors who worked with the Red Cross, in Nigeria, during the Biafra secession war, were shocked by the ongoing genocide and frustrated by the silence they were held. Therefore, Raymond Borel and Philippe Bernier, journalists of the medical journal “Tonus”, launched an appeal to create a team of doctors ready to help those suffering in the most serious catastrophes. Their dream was to take a step further than the traditional principles of humanitarian intervention: *they propose to combine immediacy and professionalism with independence and testimony. Saving lives and taking care of, but also telling and reporting. Being attentive and respectful witnesses of the events that populations undergo/suffer in contexts of poverty, war epidemics and natural disasters.*

In these last more than 40 years, epidemics, conflicts, and natural disasters remained, as in previous centuries, the elements that have affected the lives of millions of people, even if much has been done in terms of identifying needs in relation to events and in drawing up rules on human rights, ethics and humanitarian law. The health needs and the short, medium and long-term consequences are in fact different in relation to the type of event in question:

1. *Extreme poverty*
2. *Emergency situations*

1. Extreme poverty situation

After a prolonged decline, the number of undernourished people rose from 777 million in 2015 to 815 million in 2016, mainly due to conflicts and drought and disasters linked to climate change. Conflict, climate change and growing inequalities add additional challenges. To provide access to health service in this situation is extremely difficult.

The poor suffer worse health and die younger. They have higher than average child and maternal mortality, higher levels of disease, more limited access to health care and social protection, and gender inequality disadvantages further the health of poor women and girls. For poor people especially, health is also a crucially

important economic asset. Their livelihoods depend on it. When a poor or socially vulnerable person becomes ill or injured, the entire household can become trapped in a downward spiral of lost income and high health care costs. Poor people are more vulnerable to this downward spiral as they are more prone to disease and have more limited access to health care and social insurance. Investment in health is also increasingly recognised as an important, and previously under-estimated, means of economic development [1].

As the Commission on Macroeconomics and Health (CMH) of the World Health Organization (WHO) has shown, substantially improved health outcomes are a prerequisite if developing countries are to break out of the circle of poverty [1].

They include both public services, private for-profit and not-for-profit services (NGO), formal and informal services, as well as traditional health care, and home/family-based care.

This opens up the problem related to the ability of the government of Low and Medium Income Country (LMIC) to have the skills, as well as the means, to start health access programs for people below the poverty line. This is strongly related to the stability/instability conditions of the country or of the regions of the country itself, where the presence of belligerent groups makes access to care even more difficult.

In these countries, a possible approach is represented by the formulation of specific intervention projects, such as vaccination projects, maternal child screening, child malnutrition projects and communicable diseases prevention. And in case of belligerent contexts by the ability of humanitarian organizations to negotiate a suspension of fighting for the vaccination campaign (measles, poliomyelitis) or for the distribution of drugs, for example against TB, HIV.

Returning to the concept of poverty, identifying the most vulnerable groups must not take into account only the income-based definitions of poverty alone, which rarely capture their complexity or their gender dimensions [2]. As just said, in the assessment of poverty, which heavily affects access to health care, it is a mistake to consider only income based definition of poverty.

Better results give the multidimensional approach to poverty, developed in the “*Oxford Poverty and Human Development Initiative*” (OPHI) at the Oxford University. This index is made up of several factors that constitute poor people’s experience of deprivation, such as poor health, lack of education, inadequate living standard, lack of income (as one of several factors considered), disempowerment, poor quality of work and

threat from violence. This multidimensional measure can incorporate a range of indicators to capture the complexity of poverty and better inform policies to relieve it, and to set up and to formulate adequate projects for eradication/reduction of poverty and access to appropriate care [3] (Fig.1).

The activity of MSF in the context of extreme poverty is expressed through support for basic medicine and surgery, vaccinations, prevention, nutrition, maternal and child health, psychological support of people in need and training for local staff.

In the last 20 years, MSF has played an important and continuous campaign to guarantee the access to drugs and vaccines and the year 2019 marks the twentieth anniversary of this ongoing campaign. The Access Campaign’s mission remains as relevant and needed as ever, in support of constantly evolving MSF operations and in the face of current global public health policies and trends.

2. Emergency situations.

The effects of armed conflict and natural disasters on global public health are widespread. Conflict and natural disasters may lead to the displacement of large populations into temporary settlements or camps in tents, with overcrowding and inadequate safe water and sanitation, and increased exposure to disease vectors during the acute phase of the emergency.

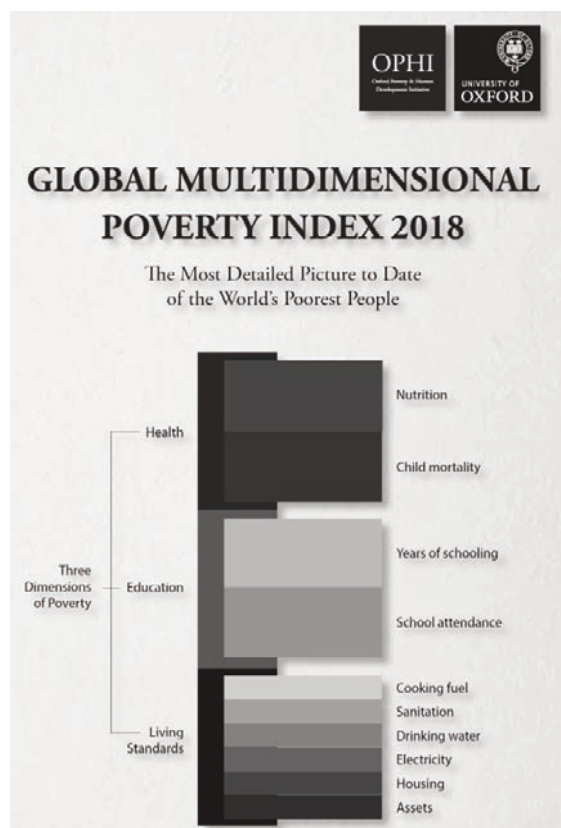


Figure 1 - The three dimension of poverty

Both lead to disruption of disease control programs and collapse of health systems in the countries involved in war or natural disaster. The global trend related to the forced displacement of 2017, published by UNHCR in June 2018, shows a continuous increase in the number of people who have been forced to leave their homes.

For an assessment that gives the overall dimensions of the problem it is essential to analyse the data published annually by UNHCR. The global trends report, published every year in June, to analyse the change in UNHCR populations, is fundamental to understand the ongoing crises. UNHCR counts and tracks the numbers of refugees, internally displaced people, people who have returned to their countries or areas of origin, asylum seekers, stateless people [2].

The global number, as evident in Figure 2, has passed in 10 years, from over 40 million in 2007, to just under 70 million people in June 2017 (68.5 million).

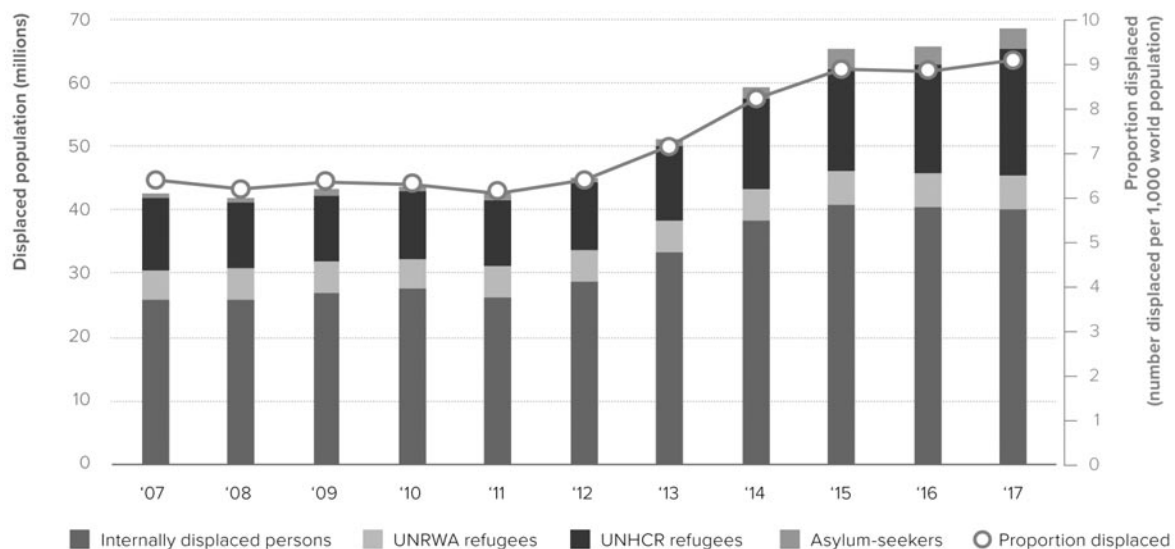


Figure 2 - Trend of global displacement and proportion displaced 2007/2017 [4].

It is evident that such a large number of people represents an overload for international protection systems provided for by humanitarian laws, difficult to sustain in time [4].

Many studies explore the link between conflicts and health aspects of human security, infectious disease epidemics, as illustrated in the UN Report *"A more secure world: Our shared responsibility"*: "poverty, infectious disease, environmental degradation and war feed one another in a deadly cycle" [5].

Health security is an important dimension of human security, as good health is "both essential and instrumental to human survival, livelihood and dignity".

Good health of a population is also important for social cohesion and stability [5]. It is estimated that more than 1.5 billion people live today in regions affected by conflict. Conflicts cause substantial human casualties and destruction of healthcare system resources (Fig. 3) [6].

Human security is increasingly being adopted as a doctrine to guide foreign policies and international development assistance, as well as a policy tool for planning in the fields of security, development and humanitarian work.

In this framework MSF provides assistance to population in distress, to victims of natural or man-made disaster and to victims of armed conflict. They do so irrespective of race, religion, creed or political conviction. MSF observes neutrality and impartiality in the name of universal medical ethics and the right to humanitarian assistance and claims full and unhindered freedom in the exercise of its functions. Members undertake to respect their professional code of ethics and maintain complete independence from all political, economic or religious powers. As volunteers, members understand the risk and dangers of the missions they carry out and make no claim for themselves or their assigns for any form of compensation other than which the association might be able to afford them. try to provide high- quality care and to act always in the best interest of patients, to respect their confidentiality, their right to make their own decision and above all, to do them no harm. When medical

assistance alone is not enough, provide shelter, water and sanitation, food or other services. Each year, the International Activity Report provides a recap of the field work. The report gives details on our activities in each country, provides global financial and operational information, and reflects on the major challenges we faced over the year. In 2017 MSF ran 462 projects in 72 countries. Treating the wounded and responding to basic health needs, malnutrition and outbreaks of infectious disease, MSF provided lifesaving care to those caught up in conflict as health systems collapsed and living conditions deteriorated. Where we were unable to secure direct access to those trapped at the heart of the violence, in places such as Myanmar and Syria, we focused our assistance on those who had escaped [7].

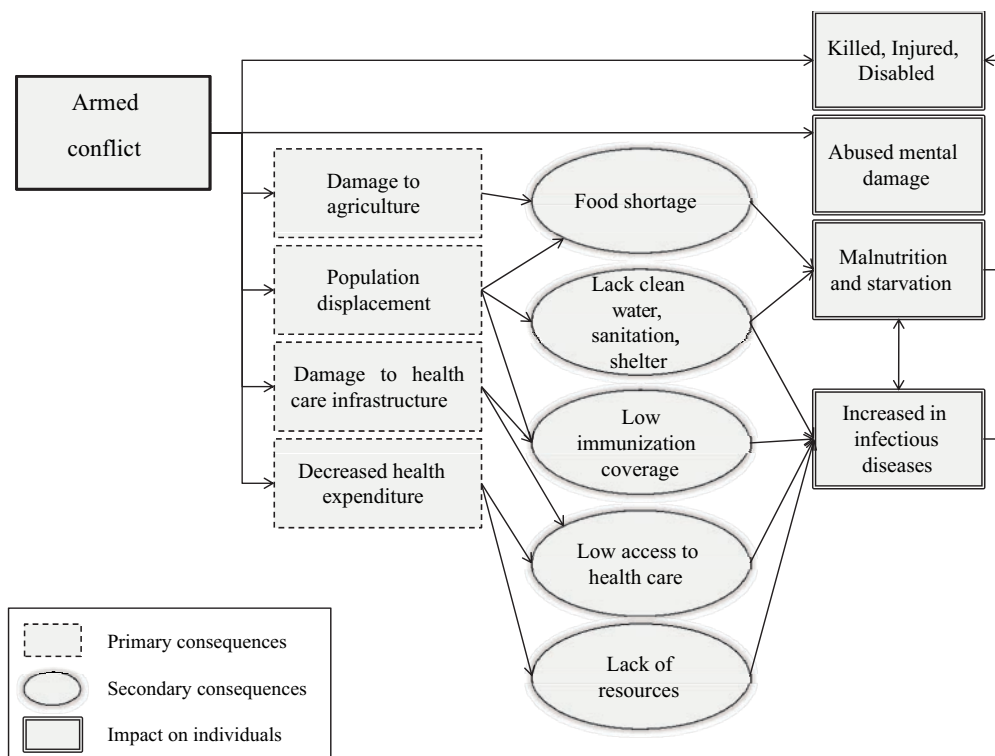


Figure 3 - Conceptual framework on the impact of armed conflict on human security [6].

Context of intervention in 2017: stable context 38% (176 projects); armed conflict 35% (163 projects); internal instability 25% (117 projects); post conflict 1% (6 projects)

Location of intervention in 2017: Africa 57% (262 projects); Middle East 18% (82 projects); Asia 13% (61 projects); Europe 6% (28 projects); America 6% (26 projects); Pacific 1% (3 projects).

Next to the health services, whose number is enormous in terms of medical examinations, surgical interventions, vaccinations, to guarantee human security, in all MSF projects, great attention is given to permit to the population access to water and sanitation. Safe water and good sanitation are essential to medical activities, and MSF teams make sure there is a clean water supply and a waste management system in all the health facilities where it works. Staff conduct also information campaigns to promote the use of sanitation facilities and ensure good hygiene practices [7].

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Universal access to quality-assured essential medicines

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The concept of “essential medicines” was developed by the World Health Organization (WHO) in the ‘70s of the previous century, in the frame of the broader efforts deployed to achieve access to health for all, through primary health care [1].

Essential medicines are those that satisfy the priority health care needs of a given population, thus they should be available within health systems at all times, in adequate amounts and dosage forms, as quality-assured formulations, and at an affordable price. They are selected based on disease prevalence, efficacy, safety, and (for comparable profiles of safety and efficacy) comparative cost-effectiveness [1]. To support countries in the implementation of this policy, the WHO issued in 1977 the 1st Model List of Essential Medicines, and in 2007 the 1st Model List of Essential Medicines for Children. Both are regularly updated according to a standardized and transparent process [2]. At the end of the previous century, more than 150 WHO member states had their own national list. Even if it is already more than 40-year old, the concept of essential medicines is still very pertinent, and it is explicitly referred to in the Sustainable Development Goals (SDGs). In particular, the indicator 3.b.3, focuses on the “proportion of health facilities with a core set of essential medicines available and affordable on a sustainable basis”.

Unfortunately, various (often interlinked) obstacles were and are still preventing an effective implementation of the essential medicines policy, in particular when it comes to fragile health systems and to socio-economically vulnerable populations. Among these obstacles, we can mention the lack of quality assurance along the supply chain; the high prices of innovative essential medicines; the lack of research & development for neglected tropical diseases; the poor prescribing practices and irrational use; and the lack of health insurance in most low- and middle-income countries (LMICs). In the next sections, we will briefly discuss the first two cases, namely the lack of quality assurance along the supply chain, and the high prices of innovative essential medicines.

Lack of quality assurance

Medicines are expected to *benefit* patients, and *not to harm* them. Therefore, they must have an adequate profile of efficacy and safety; an acceptable risk: benefit ratio; and they must be manufactured in compliance with Good Manufacturing Practices and other technical standards [3]. Failure to do so will result in avoidable *risk* or *harm*. For instance, poor manufacturing practices may result in under-dosing or cross-contamination; poor-quality excipients may result in toxic contaminants; poor-quality packaging materials may result in accelerated degradation of the active ingredient; the lack of bio-equivalence studies can result in decreased efficacy, etc. Unfortunately, the rapid globalization of the pharmaceutical market that characterized the two last decades has led to a situation of multiple standards: the quality of medicines is not uniform worldwide, but it largely depends on the level of income and of regulatory supervision in the country of destination [4].

Problems abound particularly in LMICs, where many National Medicines Regulatory Authorities (NMRAs) lack the resources and capacity needed to verify the quality of medicines manufactured, imported, and distributed in the country. If adequate standards are not implemented, medicines can be non-effective (for instance, because the active ingredient is under-dosed, or degraded, or insufficiently bio-available) or even toxic (for instance, due to cross-contamination, toxic impurities in high concentrations, lack of sterility etc.). These problems result in harm to individuals, namely therapeutic failure or direct toxicity; to public health, i.e. emergence of resistances; and to health systems (increased morbidity and mortality, erosion of trust). In absence of strong post-marketing surveillance systems, unfortunately, quality accidents and the resulting harm may go undetected [5].

Poor-quality medicines include *falsifications*, which are deliberately or fraudulently misrepresented with regards to identity, composition or source, and always result from a criminal activity; and *substandards*, which are authorized by the NMRA and are legally present in the supply chain, but fail to meet adequate standards, due to poor manufacturing and quality control practices that are not detected by the regulators. These definitions have been formally approved by the 70th World Health Assembly in 2017, and at the end of the same year the WHO

estimated that at least an average of 10.5% of medicines are substandards or falsified in LMICs.

Medicines may also *degrade* and become substandard along the supply chain, if compliance with Good Distribution and Storage Practices is not assured. Again, it is up to the NMRA to require compliance with these standards; and again, NMRAs in LMICs may lack the resources for a stringent supervision of the quality systems of pharmaceutical purchasers and distributors [5]. Difficulties are compounded by the fact that various intermediate actors, such as some international brokers, de facto escape any regulatory oversight [4]. Poor distribution and storage practices almost invariably result in quality problems, because inadequate temperature and humidity conditions will cause accelerated degradation of any medicines, while lack of adequate cold chain will cause accelerated degradation of particularly heat-sensitive products such as oxytocin, insulin and vaccines [6]. Poor stock planning and management may also cause stock-outs of essential and life-saving medicines or, on the contrary, overstocks and waste of financial resources, in addition to the logistic challenges faced to safely manage the destruction of expired medicines in resource-limited settings.

High prices of innovative medicines

It is estimated that in the year 2000, only one in a thousand persons living with HIV in Africa had access to the antiretroviral (ARV) tri-therapy. This was in first place due to the fact that ARVs were the first-ever life-saving medicines protected by patents, and thus under a commercial monopoly: the World Trade Organization (WTO)'s Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) had laid out in 1995 the minimum standards for the protection of intellectual property, including an obligation for all Member States to provide pharmaceutical product patents [7]. The patent restrictions prevented countries, donors and implementers from using generic ARV, even if these were becoming available from countries like India, for which the deadline for TRIPS implementation was in 2005. The originator companies (that controlled the patents) produced small quantities for the needs of high-income markets, at an average price of 10,000-15,000 dollars per person per year.

At that time, the joint effort of activists, civil society, medical and patients' association paved the way toward a more flexible interpretation of the TRIPS agreement. In 2001, the WTO Ministerial Conference adopted the Doha Declaration on TRIPS and Public Health, affirming the sovereign right of governments to take measures to protect public health, including the use of compulsory licensing (that enables a competent government authority to license the use of a patented invention to a third-party or government agency without the consent of the patent holder). The Doha Declaration also allowed least developed countries not to grant or enforce patents on medicines before 2016 (a deadline later extended to 2033). When the Indian company Cipla announced that it could supply triple-therapy ARVs for less than a dollar a day, it became evident that generic ARVs had the potential to allow scaling up the life-saving treatment to those in need in LMICs. However, purchasers needed assurance that quality of the generic ARVs was acceptable. To address this urgent need, the WHO created in 2001 the Medicines Pre-qualification Programme, that is a transparent process to review the safety, efficacy, and quality of such products; and in 2002, it included the ARVs in the Model List of Essential Medicines. These and other measures allowed an impressive upscale of ARV treatment in LMICs, even if universal coverage is still to be achieved [8].

Sadly, the lessons learned from HIV has not been used to build a more structural approach for ensuring early universal access to all new and innovative essential medicines. In 2015, 2017 and 2019, the WHO added several innovative medicines for cancer, tuberculosis and hepatitis C to its Model List. Being "essential", these medicines should become rapidly available and affordable to all those in needs. But being under patent in the key-countries with manufacturing capacities (including India), they are very highly-priced, and out-of-reach for many patients, and for the health systems that serve them [9].

Noteworthy, the essential medicines policy had been originally designed as a tool for LMICs. But some new essential medicines are priced so high these days, that these prices may become unsustainable also for the health-care systems of many upper middle-income and high-income countries. For instance, sofosbuvir came to the market at a price of about 90,000 dollars per patients, why the prices of innovative cancer medicines are spiraling out to levels unaffordable for most health systems worldwide (not to mention the affordability to patients and households). The Expert Committee on the Selection and Use of Essential Medicines explicitly called on WHO, in its 2015 report, to "take actions at global level to make these medicines more accessible and affordable". The inclusion in the WHO Model List "should be grounds for governments and other stakeholders to take action to ensure that the medicines are made available and affordable".

Perhaps, the time is coming to recognize that the paradigm for essential medicines has shifted: differently from the ARV crises at the beginning of this century, which was limited to LMICs, the call for access to new, innovative essential medicines is now equally addressing policy makers and health systems in poor and affluent countries; and it requires a strong solidarity effort.

The way forward?

The SDGs call for the achievement of universal health coverage by the year 2030, and this implies universal

access to affordable and quality-assured essential medicines, vaccines and other medical products. But much more is to be done compared to today *status quo*. When it comes to quality assurance, at least 10.5% of medicines circulating in LMICs are of poor quality according to the 2017 estimations of the WHO. Nonetheless, many global health stakeholders are still underplaying or ignoring this problem, and insufficient efforts are being done to strengthen regulatory authorities in LMICs, to secure the private, public and non-for-profit supply chains, and to protect the most vulnerable patients and communities from poor-quality medicines [10]. When it comes to affordability of new, innovative essential medicines, the patent-related monopoly still prevents widespread access, and a public policy response is urgently needed to address the intellectual property challenges associated with essential medicines, at a global level. In addition, health and regulatory systems need to become sufficiently robust to develop a research & development agenda based on unaddressed needs globally (e.g., including neglected tropical diseases); to strengthen and coordinate supply chains; to take up new treatments and deliver them safely; and to build health insurance schemes that allows everybody to receive essential and life-saving treatments for free [7].

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Current challenges in maternal and child health in LMICs

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Introduction: a brief history of how the international community has addressed MCH issues

To gain a full understanding of the challenges in developing and implementing effective policies and interventions in maternal, neonatal child and adolescent health, a quick look at how the international community has been addressing MCH issues is useful to provide an insight into the historical developments in the global agenda and a better basis to understand the current challenges.

For the sake of clarity, we have arbitrarily identified four main phases over the 40-year period from the Alma Ata declaration (1978) to present. These phases do not have clear cut starting and finishing lines. Rather, they have been frequently overlapping and following a variety of patterns across countries and organizations. Although it oversimplifies the complexity of both the conceptualization and the reality on the ground, this periodization allows to identify a historical logic (which does not coincide necessarily with a content logic) behind the current strategic directions and therefore to better understand the existing needs and constraints.

The first period corresponds mainly to the decade after Alma Ata, when maternal and child health (this was at that time the definition of whatever encompassed from reproductive health to adolescent health, has remained the same for decades, and in several Ministry of Health Offices it is still kept as such) was seen as a key component of Primary Health Care (PHC), together with nutrition, essential drugs, vaccines and other components [1]. Conceptually, this comprehensive system, implicitly conceived as universal, able to reach out for rural villages and urban peripheries, was the ideal system. Several countries have adopted it and many still show the remnants of this approach, for example in health centres and posts where health professionals are able to deliver basic to comprehensive MCH interventions. However, the system at that time still lacked a sound basis, made of well identified and evidence-based interventions and processes by level of care (for example clear case management guidelines and referral criteria), of numerically and qualitatively adequate personnel and commodities, and, last but not least, of managerial capacity.

Due to these and other weaknesses and inefficiencies, a more pragmatic, disease-oriented approach was developed: the so-called “Selective Primary Health Care for Disease Control in Developing Countries” [2]. This new framework advocated a more economically feasible approach to PHC by targeting only specific areas and choosing the most effective treatment plan in terms of cost and effectiveness. One of the foremost examples of SPHC was “GOBI” (growth monitoring, oral rehydration, breastfeeding, and immunization), strongly supported by UNICEF in developing nations, soon accompanied by family planning (birth spacing), female education and food supplementation (for example, iron and folic acid fortification/supplementation to prevent deficiencies in pregnant women) to become GOBI-FFF.

The selective strategy focused on the most severe health problems in developing countries, where a few diseases were responsible for high rates of infant and child mortality. Health care planning was supposed to be used to identify which diseases required most attention and, consequently, which interventions could be most effectively applied as part of primary care in a least-cost approach. The targets and effects of selective PHC were specific and supposed to be measurable. Unfortunately, this “economy-driven” approach (temporarily coincident with the World Bank and International Monetary Fund approach, which at that time was based on the “Washington consensus” economic theory about development which forced several low and middle income countries to reduce their health budgets), opened the way to a rapidly growing list of single disease programs or, at best, specific groups of diseases programs. These so-called “vertical” programs have been (and to a certain extent still are) quite favourite by big donors, which funded and logistically supported specific training, dedicated health workers, specific groups of commodities [3], data-set and targets and even managerial mechanisms, with the consequence that some of the branches of the health system tree could develop and move to reach (driven by specific and separated funds) their own specific targets but also that several other health needs were neglected and the overall functioning and development of the health system as a whole got weakened. The limitations of the vertical, essential interventions approach were emphasized by many critics and vertical programs started to

¹For the sake of simplicity we will be using this acronym instead of the official RMNCAH throughout the paper

be integrated or, at least, to include a mandatory health system strengthening component. More comprehensive lists of essential interventions and commodities for MCH, identified by level of care (community, health centre, referral) were developed [4] and started to be “packaged” along the continuum of care, particularly around childbirth due to the concentration of mortality, both maternal and neonatal, in this period.

The selective, “vertical” approach dominated the scene until well into the new millennium. The MDGs, developed in 1995, four of which indirectly or directly addressing MCH issues (poverty and hunger, gender equity, maternal health, child mortality), produced a stronger focus on MCH and called countries to increased and more comprehensive efforts in the area [4].

This third phase, which by no way can be considered over, has been characterized by improved results in terms of mortality reduction, particularly under five. Increasing focus was devoted to care around birth, with the structure of basic and comprehensive obstetric and neonatal care developed and supported with specific commodities and training. Much more efforts have been made in addressing maternal neonatal morbidity and mortality, based on evidence on much slower progress in mortality reduction as compared to post neonatal and under five mortality [5]. Global strategies have been developed focusing on maternal and neonatal health [6-7].

In 2011, a milestone document produced by WHO and other partners identified the enabling policies which are necessary to ensure good health-to young women, mothers, newborns, children and adolescents, maybe posing a conclusive full stop, at least conceptually, to the era of selective vertical interventions [8].

The most recent developments include on one side the emphasis on quality, started at the end of the past millennium, but openly recognized as a global priority only recently [9-10], and on the recipient-focused component of quality which is patient-centered care, respect and dignity for women and children, and on the other the rapidly increasing focus on early child development.

These three major strategic shifts (system approach, patient-centered care, and ECD) and their implications will be briefly discussed in the following sections.

System approach

Altogether, the major and much welcome shift which gradually imposed in global strategic directions is a system approach to MCH (and, besides MCH, to many former disease-focused programs). This means considering all system building blocks (governance and managerial capacity, financial resources, human resources, equipment and supplies, information and data management) including the more recently added “community” component of the system when identifying bottlenecks to service delivery and making plans. Furthermore, it means considering health as a matter of the whole government, in terms of addressing key aspects of the health systems, (such as financing and human resources training, recruitment and deployment) and also addressing social determinants, and particularly nutrition, education, social protection, environment and transport and many others. Multisectoral approaches are now mandatory in all country MCH strategic plans, but it should be so also at peripheral level, typically at district level.

Among all health system challenges, the lack of human resources for health is the most dramatic. Many countries have addressed this through task shifting from the higher to the lower-level health professionals, and the role of Community Health Workers in building bridges between the system and many underserved population groups has been emphasised [11]. However, this is not the panacea. CHWs and similar health workers need to be adequately trained, selected, equipped, and feel and be seen as part of the system. Higher level health professionals remain fundamental, while they are either scarce or all too frequently absorbed by private services, which are often not accessible to the majority of the population. Ultimately, the challenge is a financial one, since there is no way to address effectively the human resource problem without increased investments. Specific indications for projects and program development include: avoiding to develop and implement MCH projects which are not solidly embedded in multi-year multisector plans or do not have realistic prospects of becoming sustainable; and investing in training institutions and programs, but within a multi-year strategy that allows to deploy and adequately remunerate health workers.

Patient-centered care

Patient-centered care has been also included as a key dimension of quality, but only over the last decade quality has started to be systematically assessed also taking into account the recipient side [12]. The right to respectful care has been fully recognized in the WHO standards for maternal and neonatal care [13] but implementing it at service level requires also a major shift in training institutions, curricula, task description, supervision and also a much stronger community awareness about rights to quality and dignity. Specific indications for project and program development comprises including components that address patient-centered care by building awareness, looking at and discussing case studies also from this perspective, developing indicators, collecting users’ views, working with professional associations on one side and with communities on the other. Patient-centered care is not only a matter of human rights , but also a key component of effective care [14].

Early child development (ECD)

Overall, globally, more than 40% of children who survive their first years cannot develop their full potential due to ill health, inadequate nutrition, emotional neglect or violence, poor opportunities to play and to access early and quality day care [15]. This is a major global problem that needs a whole of society approach, as the milestone document on Nurturing care for ECD clearly states [16]. However, the health sector plays a major role in reaching out for all families and building awareness about the need to ensure to all children the best possible start since birth [17], through attention paid to immediate bonding. Kangaroo care is a great example of nurturing care applied to neonates, since it reduces morbidity and mortality but also enhances development [18]. Traditional growth monitoring and nutrition programs should comprehend assessment and promotion of development. Tools have been developed and validated and need now to be implemented [19-20]. Specific indications may include, among others, using all contacts in health services to strengthen caregivers knowledge and skills in providing positive interactions since birth, and therefore training health professionals to show parents how to engage in development-focused practices with their children. This is particularly important during hospital stay, and for small, premature and sick newborns, malnourished children or children with disability.

Key main strategic shifts in MCH	Key concepts	Main challenges
1. System approach	Health in all policies	Implementing a system perspective and inter-sector collaboration at all levels of the system
2. Mother- and child- centered care	Equity, Quality and Dignity	Focusing on effective delivery and considering the recipients of care rights and point of view
3. Early child development	Survive, thrive and transform	Raising awareness about the need to move beyond mortality reduction and incorporating new contents in tasks and interventions

CONCLUSION

Although apparently there is no explicit link between them, the “new” strategic directions in MCH are all coherent in calling for a significant change in the way health systems, health managers and health professionals should conceive their objectives and tasks. Essentially a shift is needed from focussing only on specific diseases and intervention aimed at reducing mortality and major morbidity to focussing on people, seen as entitled to health, respectful and integrated care and opportunity to develop. In some way, we need to resume the concept of holistic, comprehensive health which was originally developed by WHO.

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Neonatology in Low and Middle-Income Countries: from theory to practice

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INTRODUCTION

The neonatal age is the period of life with the highest risk of life-threatening diseases: as reported by the United Nations Children's Fund (UNICEF) [1], an estimated 2.6 million children die during the first 28 days of life, about one half of the infant deaths occurred before 5 years. Additionally, an estimated 2.6 million babies are stillborn every year.

Noteworthy, three-quarters of newborn deaths occur in the first week of life, with the greatest risk of death in the first 24-48 hours after birth [2].

Neonatal survival is closely linked to the income level of a country. However, per capita income alone is not fully correlated with the neonatal mortality. Some countries have significantly improved survival rate by prioritizing appropriate technologies for the care of newborns, healthy newborn infants included, adopting strategies applicable even when resources are scarce.

The World Health Organization (WHO) has highlighted few critical steps to improve the efficiency and effectiveness of perinatal care [3]: facilitating the access to sustainable medical care, staff training, the application of shared "Evidence-Based" guidelines, and a reliable collection and analysis of epidemiological data with the focus on improving the "Quality of care".

CAUSES OF NEONATAL MORTALITY

Causes of neonatal deaths often act very quickly, requiring a prompt response from health professionals. The vast majority of them have preventable etiology [4]: more than 80% of neonatal deaths are the result of inadequate care for small and premature babies, complications during delivery and birth, congenital or acquired infections, and inability to start proper nutrition:

"In a rural area of the Democratic Republic of the Congo (DRC) data were collected on 1,892 births... Risk factors associated with perinatal deaths were identified... Over one-half of early neonatal deaths (n = 37) occurred during the first two postnatal days, and the most common causes were low birth weight/prematurity (47%), asphyxia (34%), and infection (8%). Neonatal mortality might be reduced by targeting interventions to improve neonatal resuscitation and care of larger preterm infants" [5].

Importantly, a rapid loss of body heat itself, due to the lack of active protection of the thermal homeostasis of the newborn may cause hypothermia in the first 48 hours of life and determine alone a multi-organ, irreversible metabolic imbalance.

The cause of death will then be attributed to the syndrome of respiratory difficulty or to pneumonia, to 'lethargy', hemorrhages or more generally 'prematurity'.

In order to avoid many of these preventable deaths, rapid access to quality perinatal care is crucial for all newborns and their mothers.

OTHER FACTORS THAT INFLUENCE MATERNAL AND NEWBORN HEALTH (MNH)

In addition to the direct causes of deaths, poverty and inequity undermine the survival of mothers and newborns [6].

Intersectoral actions such as expanding educational opportunities, improving living and working conditions, and increasing access to water and sanitation could dramatically improve health outcomes. Namely, low levels of female education can strongly impact on newborn mortality: the lack of empowerment conditionate women in seeking care, decisional autonomy, and accessing the best choices for themselves and their children's health,

resulting in critical delays.

Mortality is consistently lower in urban areas than in rural areas, with remote communities often having poorer access to care. However, rapid urbanization is associated with crowded living conditions, poor sanitation, and widespread poverty. Thus, even these urban averages mask disparities for the fast-growing poor population of urban and peri-urban areas.

Long distance to the health facility and low-household income negatively influenced caregivers' appropriateness and timely care-seeking practices.

The health care costs might be simply unaffordable for many families.

Complex emergencies, such as conflict and natural disasters, present considerable challenges to delivering MNH services and maintaining a functional health system.

The Human Resources challenge

A shortage of qualified health workers is a major constraint for accessing essential health care: in Africa, which suffers for more than 24% of the global burden of disease, and yet has only 3% of the world's health workers. Sub-Saharan Africa is the region with the lowest density of total health workers per 1,000 population: 2.3/1,000 compared to the European 18.9/1,000 population.

Even among countries in the same area, there might be an important difference in the percentage of deliveries assisted by competent personnel: in Ethiopia a "skilled attendant at birth" was present only at the 6% of the childbirths versus 55% in Mozambique 55%, 19% in Nepal and 83.4% % in Tajikistan, 26% in Haiti and 98% in Santo Domingo (UNICEF).

Cultural environment plays an important role: studies in Sub-Sahara Africa and South-East Asia [7] have shown that a high proportion of the dead neonates had received only traditional care, that precludes caregivers and parents from seeking medical assistance at all or taking neonates outside the home even if they are ill. This fact highlights the need to develop community awareness about prompt medical care seeking for neonatal illnesses and to improve access to effective health care.

In many Countries, the problem of the lack of personnel was faced delegating some of the more complex tasks to middle-level health workers with appropriate training: the "Task shifting".

For example, in Malawi, Mozambique, and Tanzania, around 90% of emergency obstetric operations, including caesarean sections are performed by "Clinical Officers".

MORTALITY, MORBIDITY AND DISABILITY

Mortality is only the top of the 'iceberg' of the effect of diseases in the neonatal age: a data analysis on Lancet [2] on neonatal deaths and disability shows that in higher mortality countries the disabilities as a consequence of preterm birth, intrapartum complications and hyperbilirubinemia are an important determinant of children handicap, while in lower mortality countries complications of prematurity become the main causes of disability.

As a result, in LMIC a large number of moderately preterm newborns survive with disability due to suboptimal quality of care and challenges in the use of technology, with a heavy impact on families and society.

WHO estimated that among the 140 million newborns born every year, about 20 million have complications requiring inpatient hospital care and about 10 million have severe complications requiring intensive newborn care to survive. Currently, less than 50% of preterm and sick newborns have access to quality inpatient neonatal services.

This is reflected in an important loss of human capital:

2.6 million neonatal deaths and 2.6 million stillbirths per year, millions of children with moderate or severe disability, millions of children with mild long-term disability, learning or behavior problems, and other long-term effects of neonatal conditions, as increased risk of non-communicable diseases, and finally impact in terms of burden for parents, families and the society.

These numbers should encourage more investment in newborn care services, including inpatient care for small and sick newborns for both the newborns of today and for the children and adults of the future.

THE GUIDELINES

Already in 1994 the WHO Technical Work Group published a document concerned the "Essential Newborn Care". It summarizes the care that must be guaranteed to every newborn in the first hours of life: an effective resuscitation when necessary, thermal protection, an 'early and exclusive' breastfeeding, protection against infections and specific prophylaxis.

These are interventions that mainly require expertise and care planning, rather than complex and expensive technologies, affordable even in 'limited resources' situations [3].

The "Standard precautions"

These are the precautions to prevent nosocomial infections acquired during childbirth or during hospitalization:

staff must systematically apply those interventions to reduce these risks, such as proper handwashing, cleaning and sterilization of the devices, the maintenance of every newborn child skin to skin with the mother, and the “Kangaroo Mother Care” for premature infants, and actively support exclusive breastfeeding.

Neonatal resuscitation

Infants who do not breathe spontaneously should receive appropriate stimulation and effective ventilation within one minute of birth.

The “triage”

Prematurity, low-birth-weight and other diseases may cause a very rapid and critical deterioration of the newborn clinical conditions. For this reason, the prompt identification of high-risk life-threatening situations, the evaluation of their severity and the provision of appropriate care are mandatory. Health facilities should have guidelines for the treatment of at-risk newborns, indicating procedures, emergency drugs, devices and equipment specific for the first intervention.

Prevention and management of hypothermia

Maintaining normal body temperature is essential for all newborns, especially those who have suffered from perinatal asphyxia and those born prematurely or low-birth-weight. Post-natal adaptation will be greatly facilitated by a prolonged ‘skin to skin’ contact with the mother, immediately after delivery, and breastfeeding. Mothers of clinically stable preterm births should be routinely offered the chance to take care of their child with the “Kangaroo Mother Care” method [8].

Prevention and management of hypoglycemia

Preventing, recognizing and treating periods of hypoglycemia in all “low birth weight” or premature infants, and in “large for gestational age” babies born to a diabetic mother, or with pathology in particular (for example those who have suffered from severe perinatal asphyxia).

Prophylaxis at birth

The administration of vitamin K for the prevention of ‘Neonatal Hemorrhagic Disease’, should always be ensured, as well as the ophthalmic prophylaxis. The risk of mortality and morbidity due to infectious diseases must be prevented by administering vaccines before discharge.

Neonatal sepsis, congenital or acquired

Because bacterial sepsis is a major cause of mortality and morbidity in newborns, every newborn (especially if preterm, or low weight, or with asphyxia) should be carefully evaluated for the presence of risk factors or to catch the first symptoms in order to receive appropriate and timely antibiotic therapy and supportive care, consistent with existing WHO guidelines.

To avoid the emergence of antibiotic resistance, proper management of antibiotics should be promoted and their use should be monitored.

Care of the newborn of a mother infected with HIV and/or tuberculosis

All small and sick infants at risk of HIV infection and/or tuberculosis should be properly assessed and receive appropriate management according to WHO guidelines.

Especially in areas with a high prevalence of HIV, the virological status in the mother should already be known at the time of delivery: infants at risk of “vertical” HIV infection should be given appropriate prophylaxis and, if needed, initiated antiretroviral therapy.

The list of clinical attention deemed necessary could be very long and articulated, including guidelines for the newborn feeding, the management of jaundice, seizures, congenital malformations, severe asphyxia, and the rational use of drugs, fluids, transfusions and the opportunity of a dedicated laboratory which uses micro blood samples for tests.

The protection from pain and chronic stress, the prevention of premature apnea, and the administration of safe and proper oxygen therapy monitoring of the O₂ saturation, are also considered important; in selected situations the implementation of Continuous Positive Air Pressure (CPAP) should be considered in the treatment of respiratory distress.

THE INTERVENTIONS STRATEGIES

Outside the strictly clinical aspects, other factors are important in determining the effectiveness of an intervention to reduce perinatal mortality and maintain a good quality of perinatal care [6]. The care for newborns cannot, in fact, be separated from care for mothers, before, during and after pregnancy.

There must be a systematic approach to the problem, with a clear political commitment to include maternal and newborn health in the National Health Policies and related development plans, and clear stewardship that pays attention to human resources, equipment and facilities.

There is the need of legislation and regulations that clearly define the mandate of health structures of different levels and the professional tasks for each role of the operators.

The childbirth will be assisted by personnel trained in the care of the mother and newborn baby from birth to discharge; and there should be a post-natal, clinical follow-up and counselling to families, at least for the first 4 weeks of life.

The Regionalization: *“a system of designing where to provide appropriate and cost-effective care, to achieve the best possible outcomes”* (WHO)- is also crucial. It consists of a rational localization of infrastructures of different levels which includes staff and medical equipment suitable for pregnancy, childbirth and post-natal care and a dedicated transport service.

The availability of trained health personnel implies a national strategy for the generation of human resources based on the development of dedicated skills for MNH, based on either in ‘pre-service’ training courses in the Universities, and on a continuous updating program ‘on the job’.

Countries must develop national evidence-based protocols and clinical standards, a national list of essential drugs (including those for MNH), guarantee the availability of equipment, medical supplies and facilities to provide qualified care, with attention to maintenance and functionality of both equipment and infrastructures.

A correct and systematic collection and analysis of perinatal epidemiological data will be opportune to start mechanisms to improve the quality of care, including supervision, monitoring and evaluation of processes and results.

Finally, in order to obtain good confidence from the Community, good communication and the participation of the families are important, always respecting human rights and dignity, newborn included. Simultaneously, mechanisms that allow the Community to influence the policy for the development of public health plans for MNH are needed.

CONCLUSIONS

Only a clear “evidence-based” definition of interventions and objectives will improve the efficacy, efficiency and quality of care for low weight, premature or pathological newborn babies, but also the correct assistance to “healthy” births.

Dedicated schools and advanced courses to train Nurses and Doctors as specialists in neonatal care, induce the establishment and support a multidisciplinary group of Perinatology of local Colleagues, will help progressively achieve these objectives.

The capabilities of the individual health provider are important and necessary, but the best quality of perinatal assistance will be the result of a constant commitment and consistency in the interventions of the various components of the entire Social and Health System.

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Malnutrition: one word, many diseases, still too many patients

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Definition

The world is facing a double burden of malnutrition. Malnutrition comprises various forms of bad nutrition, the most frequent is - until now - undernutrition though overnutrition is on the rise. Anyhow, the different manifestations may be present in the same person at different times, given that early-life undernutrition increases the risk of obesity in later life [1]. Undernutrition may regard both, macro and micronutrients, the former being insufficient intake of carbohydrates, proteins and/or lipids, the latter is a shortage of vitamins and minerals, often referred to as "hidden hunger". Most of the time children suffer from a combination of both deficiencies and the severe consequences play an important role not only in terms of under-five mortality, but also on chronic noncommunicable diseases like anaemia, rickets, and blindness - just like diabetes, cardiovascular diseases and cancer on the other extreme of the malnutrition spectrum are associated with obesity.

Malnutrition can be chronic and thus - in the case of undernutrition - lead to "stunting" in children which is expressed as low height for age, as they do not have the "material to build up" and grow tall. Acute malnutrition is usually referred to as "wasting", where a child has a low weight for age. An easy measure of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of height (in metres), though other parameters such as (especially visceral) fat distribution may be more accurate. In order to measure BMI, stunting and wasting, weight, height and age of the child should be determined and compared with the WHO-growth charts.

Epidemiology

According to the most recent data from the WHO and UNICEF for childhood malnutrition, stunting is estimated to affect 151 million children under five globally, while wasting is thought to impact 51 million, a third of them suffer from a severe form that is killing approximately 500'000 children every year. At the same time, 38 million children under five are overweight and while undernutrition is slowly decreasing, the number of children being overweight has increased more than 10% since the year 2000. Furthermore, both forms are highly influenced by the social determinants of health and overlap in many countries. The alarming increase in overnutrition is attributed to the rapid urbanization, increase in income, and unhealthy lifestyles among many others. In general, poorer socio-economic groups have higher proportions of malnutrition, whether it's undernutrition, vitamin or mineral deficiency or obesity - in low-income as well as in high-income countries. There is evidence that improvements in housing conditions including the provision of piped water into the home, may be a key factor in the elimination of chronic undernutrition [2]. Man-made catastrophes like war and the accelerating climate change also have a strong negative impact on the progress made so far in the fight against malnutrition.

A detailed map showing the important country specific differences in malnutrition data can be found at: <http://www.who.int/gho/child-malnutrition/wasting/en/>.

To underscore the global importance of malnutrition beyond premature death is the fact that childhood underweight is the top risk factor of disability, while suboptimal breast feeding, vitamin A-, iron-, and zinc-deficiency also rank among the first 20.

Clinics

Often growth faltering is already present at birth and may worsen during the first years of life. Malnutrition in mothers is responsible for low birth weight, which is a predictor for reduced infant growth. In addition, parental malnutrition leads to epigenetic modifications of infant immune and metabolic genes. While stunting is associated with neurodevelopmental defects, wasting, which is characterized by a loss of muscle and (subcutaneous) fat tissue has a higher association with mortality. The majority of the 5.400.000 children that

died in 2016 before age 5 years are associated with undernutrition. This is not surprising considered that infections (pneumonia, diarrhoea and malaria) are the main causes of death in this age group and undernutrition leads to recurrent and severe infections which may trigger chronic inflammation and enteropathy and thus establish a vicious cycle with fatal outcome. However, infections are common and severe also in people with obesity. But undernutrition affects both, the innate immune system, including the epithelial barrier function of skin and gut, microbicidal activity of granulocytes, reduced complement, as well as the adaptive immunity as demonstrated by reduced Immunoglobulin and cytokine levels and fewer lymphatic tissue [3]. In fact, opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PCP) have been described in malnourished HIV-negative patients. Undernutrition is thus the most common and deadly immunodeficiency, causing literally millions of deaths every year, well beyond the death toll of HIV, as shown in table 1.

Table 1

Epidemiology/symptoms/signs	Malnutrition	HIV
Children affected	151.000.000 [9]	1.800.000 [10]
Intestinal damage	+++	++
Disrupted skin and mucosal barrier	++	+
Leucopenia/Lymphocytopenia	+	+++
Vitamin and mineral deficiency	++	+
Immunoglobulin deficiency	++	-
Anaemia	++	+
Oxydative stress	++	+
Anorexia/Asthenia	++	++
Diarrhoea	+++	+++
Recurrent infections (no diarrhoea)	+	+++
Severe infections	+++	++
Opportunistic infections	+	+++
Infections as principal cause of death	+++	+++
Proteinuria	-	+
Vertical Transmission	++	++
Deaths	540.000 direct + >2.500.000 indirect	110.000

comparison between malnutrition and HIV

Classically in children three types of severe acute malnutrition (SAM) can be distinguished: marasmus (term used already by Hippocrates, today E41 in ICD10), which is characterized by severe weight loss due to insufficient caloric intake. In nutritional emergencies it is the most common and severe form, with a high fatality rate. It is characterised by severe wasting of fat and muscle which the body breaks down to make energy and avoid hypoglycaemia, leaving a skin and bones appearance which is especially evident looking at the buttocks where the loose skin resembles “baggy pants”. These children are often irritable and have an old man appearance. The body of a wasted child tries to conserve energy as much as possible by reducing not only physical activity (hypothermia), but also reducing the body’s response to infection.

Kwashiorkor (E40 in ICD10), was first described [4] and named in the 1930s, as a “uniformly fatal” syndrome with “oedema chiefly of the hands and feet, followed by wasting; diarrhoea; irritability; sores, chiefly of the mucous membranes; and desquamation of areas of the skin”. It’s bloated appearance is due to bi-lateral pitting oedema which can mask the underlying reduction of muscles and fat. Water retention first appears in the lower legs and feet but may become generalised (moon face). Hair is usually sparse, dry and of a yellowish colour, pigment anarchy may be seen on the skin, mostly at the legs, with ulcerations, weeping lesions and fissures,

again predisposing for infections.

Most often SAM is a mixture of both conditions, so called marasmic-kwashiorkor (E42) – a life threatening combination of both wasting and bi-lateral pitting oedema.

The individual mortality risk associated with negative weight for height, weight for age and height for age scores shows a clear increase from <-1 over <-2 to <-3 Z-scores, being highest for diarrhoea (odds ratio 9.8, 95%CI 5.2-17.9) followed by pneumonia, measles and malaria [5]. As the 44% decrease in undernutrition prevalence (from 39,3% in 1990 to 22% in 2017) is slower than the 59% reduction in the under-five mortality rate (from 93/1000 to 39/1000), the proportion of death due to malnutrition is probably increasing from 50% in 1990 to over 60% in 2018!

When it comes to micronutrient deficiency, iron-deficiency is probably the most widespread and devastating deficiency affecting up to 30% of the world population, especially those living in malaria-infested areas. In fact, chronic malnutrition is associated with more severe malaria such as high-density parasitaemia and anaemia. In addition undernutrition may have a negative impact on the therapeutic responses to artemisinin combination therapies. While Anaemia is the most easily and frequent diagnosed manifestation of iron deficiency, brain iron deficiency occurs much earlier even with normal levels of haemoglobin, as iron is prioritized to haemoglobin. As a consequence, impaired brain development and cognitive, behavioural and psychomotor deficits are well known manifestations associated with iron deficiency. Most of these changes occur during the first 1000 days of life and may not be reversible. Hearing and visual impairments have also been found. The already hampered school-performance of stunted children [6] is further compromised by these handicaps and will most probably lead to a grossly reduced family income in adult life and thus influence nutrition of future parents and again fall back on the chances of the next generation.

Vitamin B12 deficiency may further aggravate the neurological consequences of anaemia, as does reduced selenium while iodine is implicated in other well-known pathways of no less importance for the developing child. Adequate zinc is again necessary for a fully functioning immune system, as demonstrated by the increased incidence of diarrhoea and acute respiratory infections associated with insufficient levels. Zinc supplementation has shown not only to shorten diarrhoea but also to prevent recurrent episodes in the short term and is thus part of the diarrhoea treatment strategy. Vitamin A deficiency is recognized as the leading cause of blindness worldwide (and thus contributes to the vicious cycle) and also impairs immune function and cell differentiation.

Diagnosis

In children between 6- and 60-months SAM is diagnosed by a very low (<-3) weight-for-height and/or weight-for-length Z-score. Besides the above-mentioned measurements, the Mid Upper Arm Circumference (MUAC) is widely used to screen for malnutrition. MUAC measurement is cheap, easily transportable, fast and does not require extensive training; at the same time MUAC seems to be a better indicator of mortality risk associated with malnutrition than Weight-for-Height [7]. The MUAC measures the upper arm muscle mass (half way between the shoulder and the elbow) with the use of a flexible measuring tape. The tape usually is colour coded (red, yellow and green) to indicate the nutritional status of a child at a glance: 0-11,5 cm red, 11,5-12,5 cm yellow, from 12,5 cm green.

A circumference below 115 mm is considered diagnostic for severe acute malnutrition (SAM) and should lead to urgent specific treatment. However, weight for height and MUAC do not necessarily always identify the same individual and should be considered complementary. A further diagnostic sign for SAM are bilateral pitting oedema.

Treatment

All children with SAM criteria should undergo a complete physical examination to assess the presence of oedema and/or any additional medical condition or complication. According to the joined WHO UNICEF statement, SAM in children that have good appetite and no other medical complications can be managed in the community using ready to use therapeutic food (RUTF) until a 15 to 20% increase in weight is achieved. However, in order to be successful, adequate training and close supervision of the Community health workers is essential, as are financial compensation or other incentives which improve their social recognition. Furthermore, a fail-proof supply chain management is pivotal for success and - in case of therapy failure - a functioning non-bureaucratic referral system to an experienced secondary or tertiary care centre must be in place.

For those children that do not pass “the appetite test” or have medical complications or any other danger sign, or social conditions that do not allow for community management, facility-based management is necessary. A comprehensive guideline is available from the WHO website. Correction of Hypoglycaemia and hypothermia are among the first steps to be taken. Again, malnutrition being an immunodeficiency, antibiotic treatment is part of the necessary treatment, as are adequate vitamin and mineral supplements (often already integrated in the commercially available therapeutic food, otherwise to be added to the locally prepared nutrition). Patients should receive the full SAM treatment based on the sequential use of special formula food (namely milk based F75, F75 cereal, F100) before switching to RUTF and continue treatment in the community.

An overview on different replacement feedings can be found in the Cochrane library.

Children with severe acute malnutrition who are discharged from treatment programmes should be periodically monitored as there is a scarcity of data on follow-up post-discharge from SAM treatment. The limited data that exist suggest that children exhibit sustained vulnerability even after achieving nutritional cure: this includes not only relapse that may present in up to one third of the children, but also persistent stunting and a heightened morbidity and mortality risk.

Despite these guidelines the case fatality rate among paediatric inpatients with severe malnutrition is >10%, with important differences within Africa (as high as 40%) and even more in comparison with Asia. This may be due to important knowledge gaps in the treatment guidelines which do not differentiate between different settings and rely more on expert opinion than on sound scientific data. There is a clear need not only to produce, but also to use the new insight in molecular, cellular and tissue biology, in inflammatory and immune competence especially in relation to the microbiome, and its influence on anthropometric measurements and body composition in order to better understand how we should care for malnourished children in different settings all over the world [8].

Because one size not always fits all!

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Sexually transmitted infections (STI) epidemiology, classification and impact: STI control strategies

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EPIDEMIOLOGY AND CLASSIFICATION

Sexually transmitted infections (STIs) are infections which are spread predominantly by sexual contact, including vaginal, anal and oral sex. Some STIs can also be spread through non-sexual means, such as via blood or blood products. Many STIs-including chlamydia, gonorrhoea, hepatitis B, HIV, and syphilis-can also be transmitted from mother to child during pregnancy and childbirth. Other infections can be occasionally spread through sexual intercourse (Tab. 1).

Table 1 - Classification of major STIs per sexual transmission prevalence

Bacteria	Viruses	Others (parasites, fungi)
Sexual transmission highly prevalent		
<i>Neisseria gonorrhoeae</i> <i>Chlamydia trachomatis</i> <i>Treponema pallidum</i> <i>Calymmatobacterium granulomatis</i> <i>Ureaplasma urealyticum</i> <i>Haemophilus ducreyi</i>	HIV-1, HIV-2 HTLV-1 Herpes Simplex Virus 2(HSV-2) HPV HBV	<i>Trichomonas vaginalis</i> <i>Phthirus pubis</i>
Occasionally transmitted through sexual intercourse		
<i>Mycoplasma hominis</i> <i>Gardnerella vaginalis</i> and other vaginal anaerobes Streptococcus group B	HTLV-II HCV Herpes Simplex Virus 1(HSV-1) Herpes Human Virus 8 (HHV8) EBV	<i>Candida albicans</i> <i>Sarcoptes scabiei</i>
Possible oro-anal transmission		
<i>Shigella</i> spp. <i>Campylobacter</i> spp	HAV	<i>Entamoeba histolytica</i> <i>Giardia lamblia</i>

More than 30 different bacteria, viruses and parasites are known to be transmitted through sexual contact. Eight of these pathogens are linked to the greatest incidence of sexually transmitted disease. Of these 8 infections, 4 are currently curable: syphilis, gonorrhoea, chlamydia and trichomoniasis. The other 4 are viral infections and are incurable: hepatitis B, herpes simplex virus (HSV or herpes), HIV, and human papillomavirus (HPV). Symptoms or disease due to the incurable viral infections can be reduced or modified through treatment.

It is estimated that annually there are 357 million new cases of four curable sexually transmitted infections among people aged 15-49 years (Fig. 1): *Chlamydia trachomatis* (131 million), *Neisseria gonorrhoeae* (78 million), syphilis (6 million), or *Trichomonas vaginalis* (142 million).

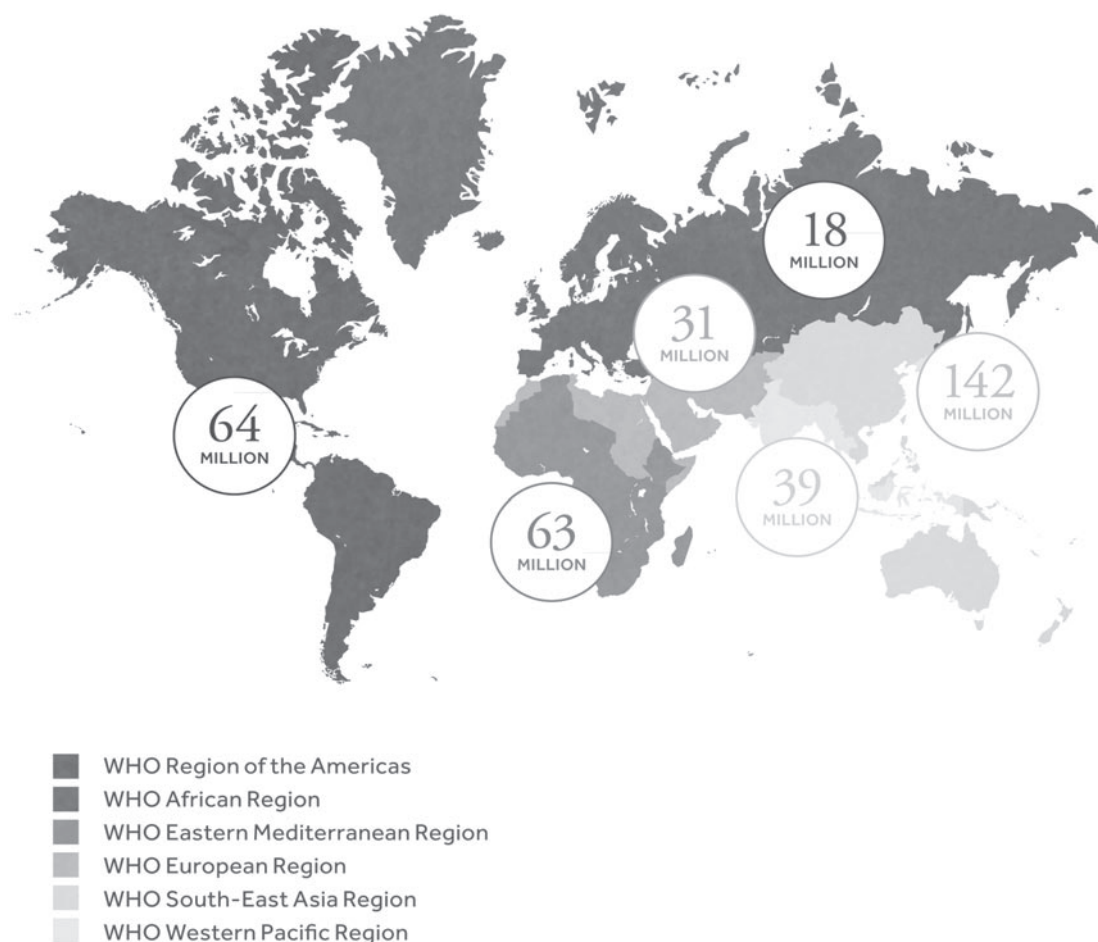


Figure 1 - Four curable sexually transmitted infections (2012 estimates). Source: Global Health Sector Strategy on sexually transmitted infections 2016-2021. <https://apps.who.int/iris/bitstream/handle/10665/246296/WHO-RHR-16.09-eng.pdf;jsessionid=79B758875F2CF84557EDFAF55079989F?sequence=1>

The prevalence of some viral sexually transmitted infections is similarly high, with an estimated 417 million people infected with herpes simplex type 2, and approximately 291 million women harbouring the human papillomavirus. The prevalence of these sexually transmitted infections varies by region and gender [1].

Sexually transmitted infections are of public health concern not only because of their high prevalence worldwide, but also because of their potential to cause serious and permanent complications in infected people who are not treated in a timely and effective way. These include congenital transmission (i.e. syphilis, HSV, chlamydia, gonorrhoea), cancer development (HPV, HBV), pelvic inflammatory disease, infertility, ectopic pregnancy and spontaneous abortion (chlamydia, gonorrhoea), and increased risk of HIV:

- Fetal and neonatal deaths - syphilis in pregnancy leads to over 300 000 fetal and neonatal deaths each year, and places an additional 215 000 infants at increased risk of early death;
- Cervical cancer - the human papillomavirus infection is responsible for an estimated 530,000 cases of cervical cancer and 264,000 cervical cancer deaths each year;
- Infertility - sexually transmitted infections, such as gonorrhoea and chlamydia, are important causes of infertility worldwide;
- HIV risk - the presence of a sexually transmitted infection, such as syphilis, gonorrhoea, or herpes simplex virus infection, greatly increases the risk of acquiring or transmitting HIV infection (by two to three times, in some populations).

Since the late 1980s, it had been found an association between HIV-positivity and evidence of past STIs (clinical history or serological evidence), suggesting the existence of an “epidemiological synergy” between HIV and other STIs. If from one side they all share a common way of transmission which implies a possible common behavioural risk, biological mechanisms seem to justify this interrelationship. For instance, STIs determining genital ulcer disease (GUD), such as HSV, chancroid and primary syphilis, increase both

infectiousness of HIV patients (as demonstrated by high level of HIV virions in ulcer exudates) and susceptibility to HIV acquisition, by disrupting mucosal integrity and recruitment and activation of lymphocytes (HIV target cells) at local level. Similarly but less clearly, non -ulcerative STIs such as gonorrhoea or chlamydial infection have been shown to increase HIV DNA shedding in genital secretions both in HIV positive males and females. Moreover, the presence of HIV increases the severity of some STIs and their resistance to treatment, such as for HPV and HSV (Fig.2) [2].

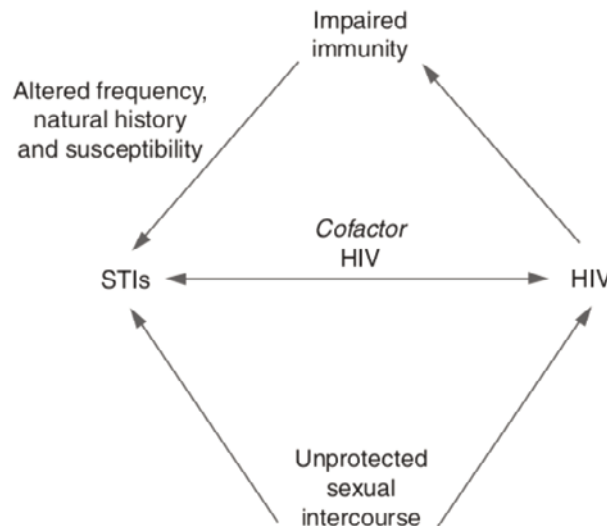


Figure 2 - Interrelationships between HIV and STIs. Source: Training modules for the syndromic management of sexually transmitted infections (https://apps.who.int/iris/bitstream/handle/10665/43275/9241593407_mod1_eng.pdf?sequence=2)

Theoretical transmission model and risk factors

To understand STI transmission Anderson has developed the ‘transmission dynamics model’. In this model, the transmission of an STI is expressed in terms of its basic reproductive number (R_0), the average number of new (or secondary) STI cases generated by an index (or primary) case in a defined population over a period of time. It has been demonstrated that R_0 is a function of the rate of partner change (c), the probability of transmission of the STI during sexual intercourse (β) and the duration of the infection (D) - summarized in the formula:

$$R_0 = \beta \times c \times D [3].$$

To control STI transmission, therefore, we should aim to reduce the basic reproductive rate by a combination of strategies, including behaviour change aiming at decreasing the number of sexual partners, increased condom use and treatment of patients with STI. The latter component of STI control programmes aims to reduce the duration of infectivity of individuals with an STD (Fig. 3) [4].

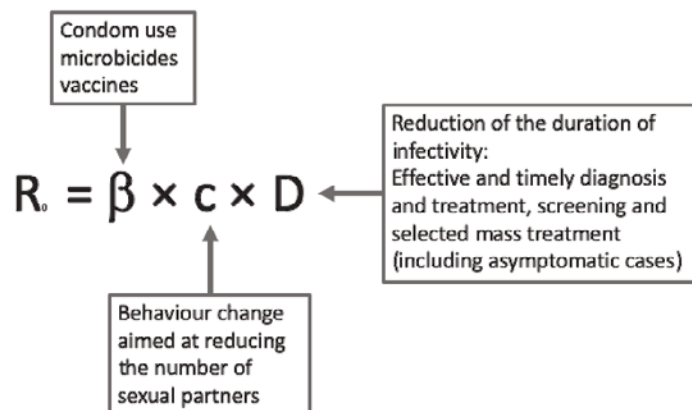


Figure 3 - Interventions aimed at reducing the basic reproductive rate

Some groups of people are particularly vulnerable to STIs and may present the highest prevalence. This may be because they are exposed to infected partners more frequently, or because they are more susceptible to getting infected each time they are exposed. Such groups include sexually active teenage girls, sex workers and their clients, men or women who have multiple sexual partners, and men or women whose jobs separate them from their regular sex partners for long periods of time, such as long-distance drivers, soldiers and migrant workers.

Either partner change rate and duration of infectivity are influenced by sex, age, biological characteristics and social influences, often combining each others. Infections enter the body most easily through a mucosal surface such as the lining of the vagina. Since the mucosal surface that comes into contact with the infective agent is much greater in women than in men, women can be more easily infected than men. Some STIs (Chlamydia and gonorrhoea) can be asymptomatic or slightly symptomatic in women in about 70-80% of cases, thus determining undertreatment (and a higher risk of transmission) and increasing the risk of sequelae. Additionally, in young girls, the cervical ectopy (a physiological condition) makes them more vulnerable to STIs than older women. Simultaneously, young women are especially at risk in cultures where they marry or become sexually active during early adolescence and tend to have intercourse with older men (having a higher rate of partner change). In most cultures, women have very little power over sexual practices and choices, such as the use of condoms. They tend to be economically dependent on their male partners and are therefore more likely to tolerate men's risky behaviour of multiple sexual partners, thus putting themselves at risk of infection, or delaying seeking care. Additionally, sexual violence tends to be directed more towards women by men, making it difficult for women to discuss STIs with their male counterparts. For all these reasons, on average, women become infected at a younger age than men.

These risk factors, read within the dynamic model, have highlighted the importance of groups of individuals who have much higher rates of sexual partnerships. These 'core groups' and their sexual partners (i.e. female sex workers and their clients, MSM/bisexual) - who may form 'bridge populations' between the core groups and the general populations (Fig. 4) - have been shown to be epidemiologically important in driving the STI and HIV epidemics in many parts of the world.

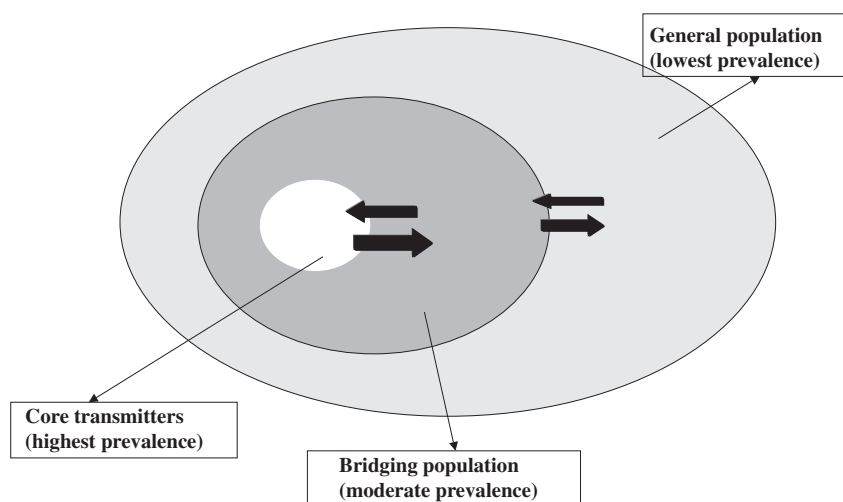


Figure 4 - The structure of sexual networks (adapted from Cates W & Dallabetta G, 1999)

Control strategies for STI

To conceptualize the strategies needed to control STIs, an "operational model" has been developed. This model identifies all the steps needed in health care services to consider an STI cured. At each step, a proportion of patient drop out and only a small fraction of STI cases are successfully treated. Proposed public health intervention aim at reducing the number of patient drop out (Fig.5).

Early diagnosis and effective treatment of STIs is an essential component of STI control programmes. The traditional method for STI diagnosis has been through laboratory diagnosis of the aetiological agent, but this approach is expensive and often results in delays in diagnosis and treatment. To address the limitations of both aetiological and clinical diagnosis in the management of STIs, particularly for patients who attend the first level of primary health care, the WHO has developed and advocated the syndromic management approach [5]. STI-associated syndromes are easily identifiable groups of symptoms and clinical findings on which the healthcare providers can base their presumptive diagnosis.

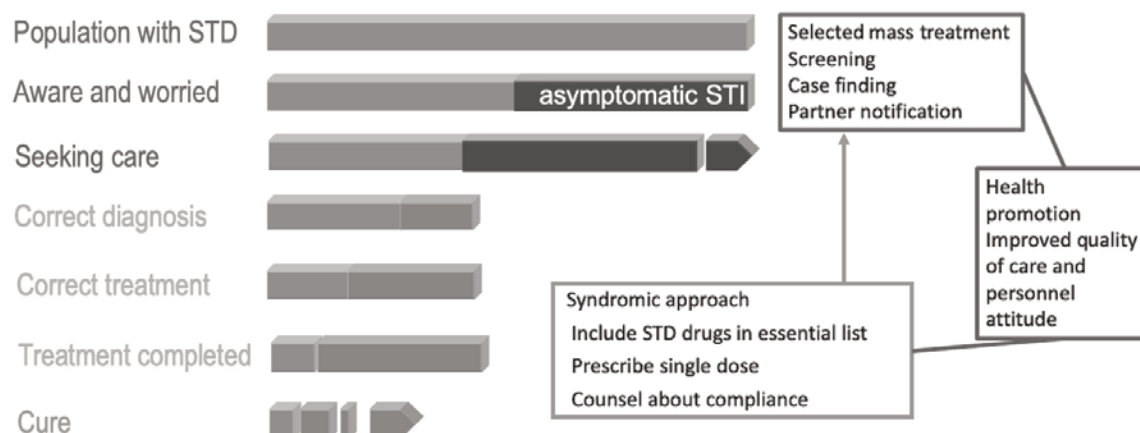


Figure 5 - Operational model and public health interventions

Management is simplified by the use of clinical flowcharts and allows time in the consultation to provide simple education messages, discuss partner notification and promote condoms. Antimicrobial therapy is provided at once to cover the majority of pathogens presumed responsible for that syndrome, in that specific geographical area. It can be adopted in a variety of settings, including STI clinics, primary healthcare facilities and family planning/maternal and child health services and private sector. There are a few main limitations to syndromic management. Firstly, the risk of over-diagnosis and treatment, closely related to local STI prevalence. In settings with low prevalence, the sensitivity of syndromic management is high but at lower specificity and cost-effectiveness. Secondly, antibiotic usage can increase the risk of antimicrobial resistance and of alteration in the normal gut flora, as in the case of gonorrhoea resistance. Finally, this approach has limited sensitivity for cervical infections in women (i.e. Chlamydia and gonorrhoea), even in setting with high prevalence. To overcome these limitations, WHO has developed a risk assessment to increase the sensitivity for cervical infections in settings where a vaginal examination with a speculum is not feasible. Indeed, to reduce the risk of treatment failure to cephalosporine treated secretive syndromes, WHO has introduced a second clinical evaluation aimed at both assessing clinical cure and collecting data on the spread of antimicrobial resistance for *N. gonorrhoeae* [6]. Partner notification (PN) is a strategy aimed at contacting patients' sexual partners by contacting them to offer screening and treatment. From a public health point of view, it aims at reducing treatment delay and at diagnosing and treating asymptomatic infections, reducing the spread of infections within the community. The most practical approach is treating with the same drugs the patient's sexual partner, with the risk of over-prescription of antibiotics. Nevertheless, benefit from partner notification seems to be less clear in case of viral infections (HSV or HPV) and only limited data have evaluated the impact of PN on prevalence and incidence of STIs in the population.

Other strategies to increase the detection of asymptomatic cases include screening in individuals not seeking health care or case finding in patients seeking care for other reasons. Examples of screening are those performed in blood donors for syphilis, HIV and hepatitis in blood donors and for HIV, syphilis in ANC attendees, or for Chlamydia in young girls.

To address the "core groups", selected mass treatment has been evaluated and proposed in high-risk groups in order to reduce prevalence and incidence of STIs and, based on the concept of "epidemiological synergy", of HIV.

Whenever feasible, vaccines are fundamental instruments to reduce the basic reproductive number of STI. Meaningful examples currently under implementation include HPV and HBV, but research efforts are ongoing to develop effective vaccines for other STIs.

Finally, efforts are needed for primary prevention directed at changing behavioural risk factors, increase health literacy and the seeking for care, especially among teenagers, which have higher rates of STIs and are more susceptible to educational interventions. Condom use, mutual monogamy and safer sex are examples of behaviour changes to implement, even during a patient's clinical evaluation, which must always include adequate counselling and educational moments.

In settings at high HIV prevalence, male circumcision has been implemented due to the proven efficacy in reducing HIV susceptibility among men and HIV male-to-female transmission, but its value in reducing other STI spreading remains controversial. It seems to impact the overall spreading of HPV, Mycoplasma and GUS but acts poorly on gonorrhoea and chlamydial infections [7].

Moving from the syndromic approach to the aetiological diagnosis: The Global Health Sector Strategy for STIs 2016-2021

Despite syndromic approach has been successfully implemented in several low-income countries, some constraints have been raised for the risk of overtreatment, the development of antimicrobial resistance (as for *N. gonorrhoeae*) and the low sensitivity to identify cervical infections in women. The shifting from the syndromic to the aetiological approach is clearly stated in the Global Health Sector Strategy for STIs 2016-2021 released by WHO [1].

The document identifies four core components of sexually transmitted surveillance: case reporting, prevalence assessment, assessment of the aetiology of sexually transmitted infection syndromes, and monitoring of antimicrobial resistance.

It focuses primarily on three infections that require immediate action for control and that can be monitored:

- N. gonorrhoeae* because of the rising risk of untreatable gonorrhoea and the risk of coinfection with other sexually transmitted infections including *C. trachomatis*;
- Treponema pallidum* with the elimination of congenital syphilis;
- Human papillomavirus with an emphasis on vaccination towards the elimination of cervical cancer and genital warts. Cost-effective interventions exist for all three sexually transmitted infections.

Despite the importance of *C. trachomatis* infection and the increasing rate of infection in adolescents, the document encourages further research and cost-effectiveness analyses to define the best strategies to control and measure chlamydia infections, but do not indicate actions for this infection.

Ending sexually transmitted infection epidemics as public health concerns by 2030 is the ambitious goal of this Strategy, and four targets to reach by 2030 have been identified:

- 90% reduction of *T. pallidum* incidence globally (2018 global baseline);
- 90% reduction in *N. gonorrhoeae* incidence globally (2018 global baseline);
- Sustain 90% national coverage and at least 80% in every district (or equivalent administrative unit) in countries with the human papillomavirus vaccine in their national immunization programme;
- 50 or fewer cases of congenital syphilis per 100 000 live births in 80% of countries.

The strategy promotes a people-centred approach, grounded in principles of human rights, gender equality and health equity, and promotes intervention for the reduction of discrimination and stigma related to STIs. It aims at accelerating comprehensive prevention efforts through scaling up evidence-based combined behavioural, biomedical and structural approaches, and supports the development of specific treatment guidelines, as those already released for syphilis, *C. trachomatis* and *N. gonorrhoeae*.

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Tuberculosis Ending the TB Epidemic

“Ending the TB epidemic is a Sustainable Development Goal target that requires implementing a mix of biomedical, public health and socioeconomic interventions along with research and innovation”
World Health Organization

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TUBERCULOSIS

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*, and one of the top 10 causes of death worldwide. The bacteria typically affect the lungs (pulmonary TB), but can also affect other sites, such as the lymphonodes, kidney, brain, spine (extrapulmonary TB). The bacteria is spread through the air when a person with pulmonary TB or throat TB coughs, talks or sneezes.

Some people develop TB within weeks after becoming infected and before their immune system can fight the TB bacteria. However, a small minority infected with the *M. tuberculosis* develops the disease. The condition in which the bacteria remains inactive is called latent tuberculosis infection (LTBI). People suffering from LTBI may get sick years later (overall about 5 to 10% of those who do not receive treatment for LTBI), when their immune system is weakened by concurring factors, such as HIV (TB is a leading killer of HIV-positive people), undernutrition, diabetes, smoking, or if they are elderly or babies.

Around the 20th century, thanks to social and economic development, TB cases and related death rates started to decline. TB mortality has fallen 47% since 1990 and its incidence has decreased by 18%. Effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014 [1]. Despite incredible advances, this progress is insufficient to reach the ambitious goal of ending the TB epidemic by 2035.

In 2017 alone, 10 million people fell ill with TB, and 1.6 million died from the disease (including 0.3 million among people with HIV). Globally, TB incidence is decreasing at a rate of about 2% per year. This needs to accelerate to a 4-5% annual decline to reach the 2020 milestones of the End TB Strategy.

Drug-resistant TB is a public health crisis, with 558.000 people contracting a form of TB resistant to rifampicin (RR-TB), the most effective first line drug, and of these, 82% had multidrug-resistant TB (MDR-TB - resistant to rifampicin and isoniazid). Furthermore, about 1.7 billion people, 23% of the world's population, are estimated to have LTBI, and are therefore at risk to develop active TB disease during their life [1].

Without a proper treatment, the mortality rate of TB is above 50%.

THE END TB STRATEGY

In the late 1800s, tuberculosis was one of the major causes of death in European countries.

While TB is regarded as a disease of the past in countries with low incidence (≤ 100 cases per million population a year) [1], it remains a major public health problem in many parts of the world.

Global efforts to control TB were relaunched in 1991, when TB was recognized as a major global public health problem. Two targets for TB control were established as part of this resolution - detection of 70% of new smearpositive cases, and cure of 85% of such cases, by the year 2000.

The first Global Plan to Stop TB (2001 - 2005) helped to steer global TB control efforts during that time leading the way to the second Global Plan to Stop TB (2006-2015) - a strategy that enables existing achievements to be sustained, effectively addresses the remaining challenges, and

underpins efforts to strengthen health systems, alleviate poverty and advance human rights (The Stop TB strategy, WHO 2006).

Several challenges remain to be overcome to end the TB epidemic.

The global response to fight TB and put an end to the global epidemic is informed by the WHO *End TB Strategy*, which was established by the World Health Assembly (WHA) in 2014. Ending TB requires implementing a mix of biomedical, public health and socioeconomic interventions, along with research and innovation.

Progress in ending the TB epidemic will depend on:

- Optimizing strategies and interventions for TB care and prevention;
- Achieving universal access to TB care and support within Universal Health Coverage;
- Investing in research to develop new, better and rights-based strategies for diagnosis, treatment and prevention of TB [2].

The *End TB Strategy*'s goal is to end the global TB epidemic by 2035. In particular, its main targets are:

- 95% reduction in numbers of TB deaths (compared with 2015);
- 90% reduction in TB incidence rate, defined as <10/100 000 (compared with 2015); and
- Zero TB-affected families facing catastrophic costs due to TB [2].

To reach those targets, the *End TB Strategy* sets out interventions and actions clustered under three pillars.

1. Integrated, patient-centred care and prevention
 - a. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups;
 - b. Treatment of all people with tuberculosis, including drug-resistant tuberculosis, and patient support;
 - c. Collaborative tuberculosis/HIV activities, and management of comorbidities;
 - d. Preventive treatment of persons at high risk, and vaccination against tuberculosis.
2. Bold policies and supportive systems
 - a. Political commitment with adequate resources for tuberculosis care and prevention;
 - b. Engagement of communities, civil society organizations, and public and private care providers;
 - c. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control;
 - d. Social protection, poverty alleviation and actions on other determinants of tuberculosis.
3. Intensified research and innovation
 - a. Discovery, development and rapid uptake of new tools, interventions and strategies;
 - b. Research to optimize implementation and impact, and promote innovations.

To ensure positive impact, all interventions must build on principles of government stewardship, strong coalition with civil society, human rights and equity, and adaptation of the strategy at country level with global collaboration [2]. Monitoring progress is essential to assess the global situation and define future corrective actions to be taken. A global tuberculosis surveillance system is essential to ensure regular monitoring through standardized methods and indicators such as incidence, prevalence and mortality.

For planning, monitoring, and evaluating progress, the *End TB Strategy* defines milestones for 2020 and 2025, required for near-term strategy, as well as targets for 2030 (SDGs) and 2035 [2].

	MILESTONE		TARGET	
	2020	2025	2030	2035
Reduction in number of TB deaths	35%	75%	90%	95%
Reduction in TB incidence rate	20%	50%	80%	90%
Percentage of TB patients and their households experiencing catastrophic costs due TB	0%	0%	0%	0%

To reach the 2020 and 2025 global milestones, two conditions are required:

- Globally, the annual decline in the TB incidence rate needs to accelerate from 2% per year in 2015 to 6% per year by 2020 and 10% per year by 2025;

- A reduction in case fatality ratio from around 16% in 2015 to 10% in 2020 and 6% in 2025 (this last corresponds to the average achieved in recent years in high-income countries) [2].

Achieving the 2030 and 2035 targets, the following conditions have to be fulfilled:

- Achievement of all the 2025 milestones;
- Around 2025, new tools that can substantially reduce the risk of developing TB disease among people who have LTBI must be available, and then scaled up the TB incidence rate falls at an average rate of 17% per year. The new important tools are an effective post-exposure vaccine, a more effective treatment and better tests for diagnosis of LTBI;
- Immediate investment in research and development throughout the period 2016-2025 [2].

Lastly, in May 2019, The World Health Organization has released a multisectoral accountability framework (MAF-TB) to accelerate progress to end the TB epidemic. The framework aims to support the process of defining who is accountable, what they are accountable for, and how they will be held accountable, at country and local levels, as well as at regional and global levels. The MAF-TB provides guidance on four components that form a cycle for strengthening accountability: Commitments, Actions, Monitoring and Reporting, and Review (Multisectoral accountability framework to accelerate progress to end tuberculosis by 2030, WHO 2019).

TUBERCULOSIS VULNERABILITY AND ECONOMIC BURDEN

There is a close relationship between tuberculosis and structural factors such as socioeconomic inequalities, discrimination, poverty, malnutrition, and weaknesses in health systems [3].

These conditions can be clustered in three categories: individual biological factors (e.g., immunodeficiency states), social and economic circumstances (e.g., crowding, poverty, poor nutrition), and environmental and institutional factors (e.g., silica dust, poor ventilation).

Economically poor and vulnerable populations - migrants, homeless, imprisoned people and substance users - are at greater risk to develop TB and to have worse treatment outcomes than the general population.

Currently, more than 95% of all TB cases and deaths occur in low- and middle-income countries, particularly in South-East Asia, Africa, and the Western Pacific. Additionally, thirty countries designated by WHO as high burden countries (HBCs), collectively account for approximately 87% of new TB cases globally [1]. TB cases are particularly frequent in regions of high HIV prevalence and cause around one-third of all AIDS deaths globally. In sub-Saharan Africa alone up to 70% of people living with HIV have *M.tuberculosis* infection [4]. Rates of TB can be considered as good predictors of a society's wellbeing. In particular, poverty may drive the transmission and development of TB through its influence on living conditions (overcrowded housing and poorly ventilated places), delayed diagnosis and increased vulnerability owing to malnutrition and/or HIV infection [5].

TB can be considered a poverty trap: poverty is both a cause and a consequence of tuberculosis.

Studies demonstrate that: between three and four months of work per year are lost due the disease; lost earnings amount to 20 to 30% of annual household income; and families of persons who die from the disease lose about 15 years of income [4].

Poverty and TB trigger a vicious cycle: poor people are among the most vulnerable groups; TB decreases people's capacity to work, and adds treatment costs, exacerbating their poverty. Meanwhile, the poor receive inadequate health care, preventing even the diagnosis of their tuberculosis. Evidence shows that poor people are two to three times more likely than other income groups to self-medicate, thus increasing the risk of drug-resistant TB strains [4].

On the basis of the above consideration, TB is not merely a public health problem, but also a human rights issue. The acknowledgment of this correlation can increase awareness of the importance of social determinants of health as risk factors of TB.

Universal Health Coverage

“Universal health coverage is the single most powerful concept that public health has to offer.”

Dr Margaret Chan

Across the globe, at least half of the population still do not have full access to essential health services. Over 800 million people spent at least 10% of their household budgets to pay for health care. Furthermore, about 100 million people are pushed into extreme poverty¹ because of out-of-pocket health costs [6].

Defending the right to health and ensuring access to quality essential health-care services, all UN Member States have agreed to achieve universal health coverage (UHC) by 2030, as part of the Sustainable Development Goals - SDG 3.8 “Achieve universal health coverage, including financial risk protection, access to quality essential

¹Defined as living on 1.90 USD or less a day

health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all".

UHC is built on two pillars: the WHO Constitution (1948), which declares that health is a fundamental human right, and the Health for All agenda set by the Alma Ata declaration (1978).

Universal health coverage (UHC) means that all people and communities can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship [6].

This definition of UHC embodies the principle of *equity*, which postulates that health-care services must be affordable and reachable by everyone who needs them, not only by those who can pay for them.

Furthermore, the *quality* of health services should be good enough to ensure an adequate response to those receiving them. Achieving UHC should protect people against financial-risk due to the cost of using services.

UHC is a continuous process that changes depending on shifting demographic, epidemiological and technological trends and people's expectations. UHC is an investment in human beings and capital, supporting sustainable economic growth and development. Adhering to the UHC principles means taking steps towards equity, development priorities, social inclusion and cohesion [6].

The targets *set out by the End TB Strategy*, in particular the target "no family is burdened with catastrophic expenses due to TB", can only be achieved if TB diagnosis, treatment and prevention services are provided towards UHC.

To achieve equity, and to make progress towards the SDGs and the *End TB Strategy* goals, there is a need to identify vulnerable groups, evaluate their needs, available services and barriers to access, to establish priorities for action based on needs, effectiveness, feasibility and resources.

SOCIAL PROTECTION

Every year, about 100 million people experience poverty because of the financial burden of disease. Tuberculosis is an example of a disease that can significantly contribute to the disease poverty trap.

Over the past two decades, access to affordable TB care services has considerably expanded, thanks to national efforts and global financial support. Nonetheless, many TB patients still face very high direct and indirect costs, which can put them at risk of financial ruin.

The *End TB Strategy* has a particular focus on preventing TB by addressing its social determinants, including poverty alleviation policies and social protection programs.

Social protection is defined as "nationally defined sets of basic social security guarantees which secure protection aimed at preventing or alleviating poverty, vulnerability and social exclusion" ("Social Protection Floors Recommendation." ILO, 2012) as well as "income replacement and social support in the event of illness" (The Social Protection Floor, 2009).

It means protection against poverty, social exclusion, lack of affordable access to health care, and lack of work-related income.

Examples of social protection programs related to TB include sickness insurance cash transfers, free or subsidized health care, food assistance, disability grant, maternity leave, housing subsidies.

The financial burden of TB is not merely related to direct health expenses. Income losses constitute a larger financial burden than the direct medical costs: medical and non-medical costs accounted for 20% each of the total expense, while income losses accounted for 60%.

The total TB-related costs for patients accounted for more than half a yearly income.

Economic support in combination with other types of assistance, has been associated with increased uptake of TB services, improved adherence to treatment of LTBI [8] and improved outcomes of treatment for drug-susceptible and MDR-TB [9].

A recent study analyzed the SDG data repository and the WHO global TB database for 192 countries to explore how achievement of SDG 1² could affect TB incidence. It was estimated that ending extreme poverty could reduce global TB incidence by 33% by 2035, while expanding social protection coverage could reduce incidence by 76% by 2035. Full achievement of SDG 1 could thus have a substantial impact on the global burden of TB [10].

Social protection programs exist in most countries, but may not be fully implemented and effective because inadequate financing or insufficient capacities of social welfare systems, or because they do not include TB patients among those eligible [11].

In order to achieve the ending TB goal, it is essential to increase preventive interventions that reduce people's vulnerability for TB infection.

²Eliminating extreme poverty and ensuring nationally appropriate social protection systems and measures for all

“Everyone with TB should have access to the innovative tools and services they need
for rapid diagnosis, treatment and care.
This is a matter of social justice, fundamental to our goal of universal health coverage.
Given the prevalence of drug-resistant tuberculosis, ensuring high quality and complete care
will also benefit global health security.
I call for intensified global solidarity and action to ensure the success
of this transformative End TB Strategy.”
Dr Margaret Chan

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Leprosy

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Leprosy or Hansen disease is a chronic infectious disease caused by *Mycobacterium leprae*, which develops in susceptible individuals, and predominantly affects the skin and peripheral nerves. The disease is curable, but if not adequately treated it can cause impairments and permanent disabilities.

Leprosy in the world. World data are published annually in the Weekly Epidemiological Record (WER) of the World Health Organization (WHO) [1]. The annual total number of new cases, after a significant decrease in the first five years of this century, remains more or less stable (about 200.000 new cases each year). The three countries with the largest annual number of new cases are India, followed by Brazil and Indonesia, which account around 80% of the new caseload globally. Other countries with a high number of new cases (> 1.000) are Bangladesh, R. D. of Congo, Ethiopia, Madagascar, Myanmar, Nepal, Nigeria, Philippines, Sri Lanka, and Tanzania. According to the WHO estimates, in the world there are more than three million people who, despite being treated clinically, have permanent disabilities caused by the disease and need physical rehabilitation. At the same time, the stigma still associated with leprosy remains a barrier to ending transmission, and also have an important impact on peoples' lives, long after they have been cured. Often they are vulnerable people, without the possibility of social inclusion. Considering the factors stated before, it can be said that the disease is still a public health problem in various countries of the tropical and sub-tropical belt. Currently, the main objectives of the leprosy control programs intend to stop the transmission of the disease, prevent disabilities and promote social inclusion by ending discrimination. The physical and social consequences must be considered in the operative plans, which cannot have a dimension exclusively focused on epidemiological parameters, but must become an expression of a work that intends to defend the rights and revitalize the dignity of the persons affected.

Pathogenesis. The human being is the main reservoir of *M. leprae*. From the epidemiological point of view, the people presenting the infectious clinical forms (so-called Multibacillary – MB), not in treatment, are the major source of *M. leprae*. The multibacillary person, once started treatment, is no longer contagious and therefore is no longer considered as a source of infection. The mucosa of the upper respiratory tract is the main portal of exit of the bacterium in the environment (droplet infection). Ulcerated skin lesions is another possible pathway for the elimination of mycobacteria. The bacilli eliminated in the environment represent an important factor to facilitate the contact with the bacilli: in a warm humid climate, sheltered from the sunrays, can survive even a month and a half. Certainly, degraded environments from the social and hygienic point of view help to keep active the chain of transmission of the bacillus. The main portals of entry into the human body seriously considered are the upper respiratory tract and the altered skin. The majority of the population, over 95%, will not develop the disease after the infection. In such persons the Mycobacterium enters in the organism, and is then eliminated (low pathogenicity of *M. leprae*). In a low percentage of cases, the bacillus overcome the body's defences and prolongs the status of sub-clinical infection. After a variable period, the sub-clinical infection flows into one of the clinical forms (< 1% of the infected persons), or it can evolve to spontaneous healing, depending on the degree of the immune response (Cell-Mediated Immunity - CMI). In fact, it is the CMI that determines the susceptibility of the person to the disease, conditioning the onset and expression in its various clinical forms. The incubation period is long and variable: from 2 to 5 years for the hyperergic forms (Paucibacillary cases) and from 5 to 10 years or more for the anergic forms (Multibacillary cases).

Classification. The universally used classification is the one defined by Ridley and Jopling which, based on the CMI immunity degree of the person, gathers the clinical signs in a "spectrum" with five clinical forms [2].

Cutaneous clinical aspects [3]. In the majority of cases, the first symptoms of the disease occur at the skin level. Different types of skin lesions can be found: macules, plaques, papules, nodules and diffuse skin

infiltration. Skin lesions are not itchy or painful. The so-called "immune zones", i.e. the areas of the body with higher temperature (armpit, groin), are normally not touched by the skin lesions. The clinical features of skin lesions (type and number, distribution, appearance, loss of sensation) are closely related to the degree of CMI of the person affected:

-Indeterminate (I). Outside the clinical spectrum, is the initial and transient stage of the disease (Paucibacillary/PB, non-contagious). The hypopigmented macula with rather ill-defined margins is the only cutaneous lesion present (single or multiple, of 3-4 cm), and there may be a suggestion of hypesthesia. No signs of involvement of peripheral nerves. Search for bacilli on skin smear: negative.

-Tuberculoid (TT). Hyperergic form (paucibacillary/PB, considered non-contagious). The typical skin lesions are macules, plaques, and papules. The macules, hypesthetic or definitely anesthetic, are hypopigmented with well-defined margins, very few and with unilateral distribution (one-three). Papules may be present, usually on the edge of the macular lesions, rarely isolated. Search for bacilli on skin smear: negative.

-Borderline tuberculoid (BT). Hyperergic form that marks the boundary between the non-infectious Paucibacillary/PB forms and the contagious Multibacillary/MB. The typical skin lesions are macules, plaques, and papules. The macules tend to be well defined and hypopigmented, but the marginal definition is less pronounced: reduced number in the initial stages, can be numerous when the disease progresses. The size of the macules can occupy entire body areas. A number of skin lesions greater than five and an involvement of more than three nerves means that the clinical form tends to move towards the lepromatous pole (BT multibacillary) and should be treated as such. Search for bacilli on skin smear: negative, but positive in case of downgrading to the lepromatous pole.

-Borderline Borderline or Mid-borderline (BB). Hypo-nergic form (multibacillary/MB, contagious). Typical skin lesions are macules, plaques, nodules. Macules and plaques: few in the initial phases, but then progressively increase towards the bilateral symmetrical distribution. Signs of nerve damage within the macular lesion can be present or not. The dimensions of lesions is variable, and the shapes may be very peculiar with streaming, irregular margins, presenting a polymorphic or "geographic" appearance, and typical "Swiss cheese" punched-out. Nodules red-rameic, hard-elastic, may appear between the macules and plaques. Search for bacilli on skin smear: positive.

-Borderline Lepromatous (BL). Hypo-nergic form (multibacillary/MB, contagious). Typical skin lesions are macules, plaques, nodules. The macules are numerous and assume a symmetrical disposition, without being clearly symmetrical as in the Lepromatous forms: red/rameic color, and with variable dimensions. Signs of nerve damage within the macular lesion can be present or not. As the disease progresses the macules become enlarged and infiltrated. Papules and nodules may develop, usually with sloping margins. Elastic hard nodules may appear, between the macules and plaques, especially on the face and ears. Search for bacilli on skin smear: positive.

-Lepromatous (LL). Hypo-nergic form (multibacillary/MB, contagious). Typical skin lesions include macules, plaques, nodules, and diffuse skin infiltration. Two sub-groups are distinguished: a Sub-polar lepromatous (LLS), and a Polar lepromatous (LLP). In the LLS form, the disease begins with small, widely disseminated ill-defined shiny macule, distributed symmetrically across the skin. When the disease progresses the macules infiltrate and evolve into plaques. Hard-elastic nodules, of red/rameic colour may appear. The LLP subgroup, extremely anergic, is clinically characterized by widespread infiltration of the skin, especially to the face and limbs. Often there is concern of the high respiratory tract and of the internal organs, from invasion of the bacilli. Search for bacilli on skin smear: positive.

Involvement of peripheral nerves. In all the five clinical forms, with the exception of the initial stage of the disease (Indeterminate – I), the involvement of peripheral nerves (neurotropism of *M. leprae*) is always present, representing one of the main manifestations of the disease and the cause of disability caused by the same. Are interested the skin nerves, the deep plexuses of the skin and the nervous trunks (vegetative, sensory and motor branch), which can become painful and hypertrophic, especially because of the leprosy reactions (see below). The clinic and the impairment of the peripheral nerves are presented in a different way according to the clinical form: early involvement in the hyperergic forms (damage caused by immune response), and late in the anergic forms (damage caused by multiplication of bacilli). The inflammatory process is caused by the direct action of the bacilli in the nerves, and the immune response of the organism to the presence of bacilli (leprosy reactions), or for both causes. Theoretically, all peripheral nerves may be involved, but the most affected are supraorbital nerve, V and VII cranial nerves, great auricular, median, ulnar, radial, common peroneal, posterior tibial. In the

early stages, the inflammatory process of the involved nerve trunks (neuritis) can be silent, without signs and symptoms, but as the disease progresses, the neuritis tends to become chronic and evident (especially in case of leprosy reactions) with presence of intense pain, hypersensitivity, edema, sensory loss in the innervated areas, motor alterations to muscular paralysis, causing impairments and disabilities. The loss of protective sensation is the cause of trauma, wounds, ulcers and secondary infections that can lead to permanent disability. Therefore, it is very important to perform regularly the neurological evaluation: at the time of diagnosis, during treatment and, possibly, even after the end of the same in case of neuritis or post-treatment leprosy reaction.

Pure neural form. It manifests itself with symptoms exclusively linked with the involvement of peripheral nerves, without skin lesions. Symptomatology: subjective symptoms such as burning sensations or numbness at the extremities, muscular weakness, sensory deficits, motor paralysis, abscesses in the course of the nerves. The involvement of a single nerve is more common than the polyneuritis concern.

Leprosy reactions. Such reactions are acute episodes that primarily affect the skin and nerves, being the main cause of neurological disabilities. They may occur during the natural course of the disease, during the treatment or after it. They are classified into two types: type 1 reaction, and type 2 reaction. When they occur after the end of the therapy, they must be differentiated from relapses.

-The Type 1 or "reversal" (RR). It is a cell-mediated reaction, mainly due to a change in the balance between and bacterial load. It manifests itself mainly in Borderline forms (BT, BB, BL), but also in LL (mainly LLS). Triggering causes: intercurrent infections, lysis of the bacilli caused by treatment, post-partum. Clinically, it is characterized by intense inflammation of pre-existing skin lesions (which may ulcerate), appearance of new skin lesions, and acute neuritis of nerve trunks with neural pains.

-The Type 2 or "Erythema Nodosum Leprosum" (ENL). Due to the formation of circulating immunocomplexes, with tissue deposition, and is typical of BL and LL forms. Humoral immunity is involved in the pathogenesis. Triggering causes: vaccinations, stress, and pregnancy. It is a systemic reaction with fever, asthenia, leucocytosis, proteinuria and inflammatory symptoms in various organs (skin, nerves, lymph nodes, eyes, testicles). The frequent cutaneous pattern is the Erythema Nodosum Leprosum. This presents small papules or larger nodules, which are painful and tender to touch with deep, and can be covered with blisters or ulcerate. Neurological signs are present but less dramatic than with type 1. Ocular symptoms are important: iritis, episcleritis.

Relapses. The relapses occur in people who have already finished their treatment. The main causes are the following: erroneous classification of a form MB (classified as PB), and therefore inadequate treatment; irregularities in drug intake; multiplication of drug-resistant bacilli (not yet elevated). They occur at a distance from the end of treatment (on average 5 years after MB treatment and 2 years after PB treatment). They have an insidious onset, slow in MB cases, quicker in PB cases, with appearance of skin lesions even in areas not previously involved.

Diagnosis [4]. Usually the diagnosis is clinical, despite the demonstration of the etiologic agent in skin smears (bacilloscopy), histopathology and Polymerase Chain Reaction (PCR) are used. In endemic countries, considering that in many geographic areas the availability of laboratories is limited, the diagnosis is essentially clinical. The diagnosis must be carried out as early as possible and be "certain". The disease should be suspected in persons with any of the following symptoms or signs: erythematous or rameic macules, hypopigmented skin lesions; loss or decreased sensitivity in macules; paraesthesia or numbness of the hands and feet; loss of muscular strength in the hands, feet and eyelids; pain and loss of nerve consistency; oedema/thickening of the facial skin or presence of ears nodules; painful wounds or burns of the hands and feet.

The three cardinal signs, to be identified for the diagnosis of leprosy, are the following: hypo pigmented skin lesions (patches) with loss of sensation (erythematous lesions on light skin and rameic lesions on dark skin); enlargement/thickening of a peripheral nerve trunk, pressure pain, loss of sensitivity or decreased muscular strength; presence of bacilli in skin smears (bacilloscopy). Diagnosis should be placed when at least one of the above signs/symptoms is present.

If a case of leprosy is suspected, a dermatoneurological examination must be carried out, and must remembered the eyes examination. The sensitivity of the lesions/patches (thermal, pain and tactile) should be assessed, and then observed their body distribution (monolateral or bilateral asymmetrical/symmetrical distribution). After the skin assesment is important to search for any damage of the functionality of the peripheral nerves most commonly affected. The hypertrophy of the nerves trunks must be evaluated through their examination/palpation. The alteration of the sensory and vegetative functions must be assessed in the skin areas served by the affected nerves. The onset of neurological symptomatology can also be acute (neuritis during leprosy reactions) with swelling of one or more nerve trunks, pain, loss of sensitivity, paralysis.

The detection of *M. leprae* can be carried out by:

-*Bacilloscopy (skin smear)* [5]. Cutaneous smear and staining of Ziehl Neelsen, with determination of bacterial and morphological index. It is performed with a sterile blade No 15 (5 mm long incision of the skin with a depth of 2-3 mm). It collects skin material (predominantly lymph and without blood contamination) from at least six different sites: from the two ear lobes and the margins of four different skin lesions, or from elbows and knees (so-called “cold areas”). The material collected must be laid on a slide and after staining, observed under the microscope.

-*Skin biopsy*: realized in skin lesions with 6 mm punch. In the endemic countries only used in case of diagnostic doubt.

PCR and Serology. Gene amplification performed with PCR method is useful for the diagnosis of Paucibacillary cases, and to confirm the pure neuritic forms. Serological examinations (IGM antibodies to PGLI) are also carried out, which can be useful to predict relapses in the course of therapy, but also to identify possible sub-clinical cases between contacts.

Differential diagnosis. Leprosy can be confused with various affections that present skin lesions or neurological diseases with symptoms and similar signs.

Cutaneous differential Diagnosis. The main difference between leprosy and other dermatological diseases is that leprosy skin lesions have altered sensitivity, and are not itchy.

Differential diagnosis of peripheral nerve involvement. Neurological lesions that may be confused with leprosy are various: i.e. congenital sensory neuropathy, primary amyloidosis of nerves; entrapment neuropathy; Guillain Barré; Polyarteritis nodosa (PAN), rheumatoid arthritis; Systemic Lupus Erythematosus (SLE); sarcoidosis; Lyme disease-related neuropathy; metabolic neuropathy (diabetic, alcoholic, nutritional deficiency); Infectious Polyneuropathy (AIDS, Hepatitis C, Diphtheria).

Therapy. Leprosy patients must be treated with a combination of drugs (Multi-Drug Therapy or MDT), introduced in 1982 by the World Health Organization.

MDT for MB leprosy (> 15 years of age): monthly dose Rifampicin 600 mg, Clofazimine 300 mg and Dapsone 100 mg. The course of treatment is given for 12 months. The monthly dose (blister pack) is taken at the start of treatment (Day 1) and then every 28 days for 12 months. The daily dose is taken every day for 12 months. It must be completed within 18 months or less.

MDT for PB leprosy (> 15 years of age): monthly dose Rifampicin 600 mg and Dapsone 100 mg; Daily dose Dapsone 100 mg. The monthly dose (blister packs) is taken at the start of treatment (Day 1) and then every 28 days for 6 months. The daily dose is taken every day for 6 months. It must be completed within 9 months or less. The health worker should see the patient take the monthly dose of treatment.

Leprosy treatment for children: the dosage for children varies according to their age, but they must take the same drugs for the same length of time as an adult. That means 6 months for PB and 12 months for MB.

Treatment of leprosy reactions [6]: the treatment of severe leprosy reactions (Type 1 and Type 2) is carried out with corticosteroids (1-2 mg per kg) in a decreasing dosage. At hospital level/referral centre, Type 2 reactions can be treated with a combination of prednisolone and clofazimine.

Thalidomide is an effective drug for treating Type 2 reactions, but should only be considered for patients that cannot be controlled by corticosteroids. Because of its side effects, it can only be prescribed to in-patients by physicians in referral centres. Because it causes serious damage to the developing foetus, it must never be given to female patients of childbearing age. The usual dosage is 200–400 mg daily, in divided doses, until the improvement of the reaction.

Vaccinoprophylaxis. The use of the BCG (Bacillus di Calmette and Guérin) is recommended to children exposed to home contacts. Clinical tests of a leprosy vaccine are currently implemented, designed to help treat leprosy and prevent exposed individuals from developing disease and the resulting disabilities.

Chemoprophylaxis. In several endemic countries, studies are underway to evaluate the efficacy of rifampicin chemoprophylaxis for household contacts.

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Malaria vectors in the world

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INTRODUCTION

Malaria is a severe disease caused by *Plasmodium* parasite species of which two - *P. falciparum* and *P. vivax* – are the most important for human. Despite the strong efforts made since the discovery of the aetiology, malaria is still a largely unresolved global public health problem, with 219 million cases in 90 countries estimated in 2017 (WHO Report). WHO estimates that in 2017 malaria caused about 435 000 deaths (no precise data are reported because of the poor information available on the African setting). WHO estimates that since 2000 a decrease in malaria cases and deaths of 22% and 50% respectively have been obtained. Sub-Saharan countries are the most affected with an estimated 93% of all the malaria deaths. The children aged under five years are particularly affected by the disease with about 300 000 deaths every year.

Malaria is mainly a problem of poor countries. Total funding invested to fight malaria is still very limited with an estimated 2.6 billion Euro in 2017. About 70% of these funds are donated by international public and private bodies, while governments of endemic countries provide the remaining 30%.

Plasmodium falciparum is the most dangerous agent of malaria causing more than 99.0% of malaria cases in Africa, 62.8% in South-East Asia, 69.0% in the Eastern Mediterranean and 71.9% in the Western Pacific. *P. vivax* is mostly present in the Americas, where it causes 74.1% of malaria cases [1].

PLASMODIUM LIFE CYCLE

The life cycle (Fig. 1) is quite complex requiring two hosts: the vector mosquito and the vertebrate host.

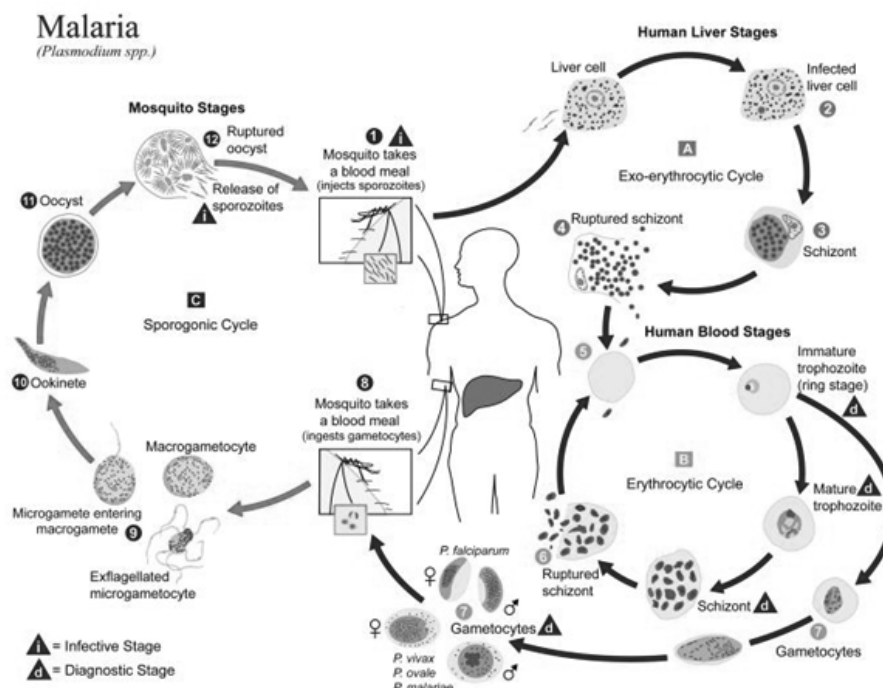


Figure 1 - Schematic representation of the *Plasmodium* life cycle (from CDC)

The parasite has both intracellular and extracellular stages within the mosquito vector and the vertebrate hosts. The female mosquito transmits many sporozoites during the blood meal. Some of them achieve the vessel system and migrate to the liver cells where they transform into schizonts which release the merozoites (this is called the exo-erythrocytic schizogony). The merozoites enter into the erythrocytes where they transform into the trophozoites, which multiply in the red blood cells and transform into the gametocytes, the sexual stages.

When the *Anopheles* female takes a blood meal from an infected human host, it also takes the male and female gametocytes which fuse in the mosquito gut to form zygotes, which develop into mobile ookinets that enter the midgut wall to develop into oocysts. Growth and division of oocysts produce thousands of active haploid sporozoites, which move through the haemocoel to reach the salivary glands, ready to pass into the new host when the mosquito will take the next blood meal. In favourable condition, the sporogonic phase, also called the extrinsic incubation period, lasts about 6-15 days mainly depending on environmental temperature (*P. falciparum* has the shortest incubation period).

It has been showed that the mosquito and the parasite benefit each other, resulting in an increase of the transmission efficiency. When infected with *Plasmodium* the mosquito has increased survival and blood-feeding rates.

VECTORS

Today more than 450 species are recognized in the *Anopheles* genus, of which around 40 are considered important malaria vectors.

Following the blood meal, the female lay batches of singular eggs floating on the water surface (Fig. 2), which in a couple of days hatch into larvae (Fig. 3) and in about a week develop in the water throughout four stages followed by the pupal stage and finally by the adults (Fig. 4).



Figure 2 - Anopheles eggs on the water

Approximately 70 of these species have the capacity to transmit human malaria parasites and 41 are considered to be dominant vector species in some geographical regions [2] (Fig. 5).

Each species of *Anopheles* mosquito has its own preferred aquatic habitat for the immature stages. For example, the *Anopheles gambiae* complex, which includes seven morphologically indistinguishable species and is the principal malaria vector in Sub-Saharan Africa, finds numerous pools of water during the rainy season. Physicochemical parameters of the breeding site water influence the sensibility to insecticides such as pyrethroids. Despite it is retained that *An. gambiae* prefers to develop in fresh oxygenated shallow and temporary waters, exposed to sunlit such as ground depressions, puddles, pools and hoof prints, it may be found in polluted waters in urban areas as well, thus increasing the risk of urban malaria. The temporary nature of breeding sites makes the colonization by predators very unsuitable.

An. gambiae also develops in rice fields containing algae, emergent grass and rice. Turbidity levels and water temperature are also important in defining the suitability of breeding sites.

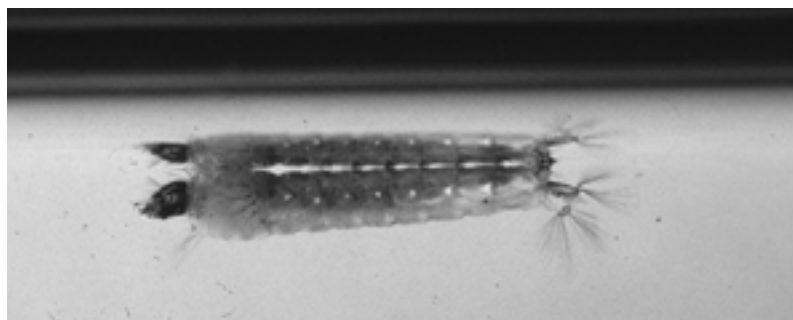


Figure 3 - Anopheles larva reflecting on the water surface



Figure 4 - Anopheles female taking blood meal (Photograph by Jim Gathany, CDC).

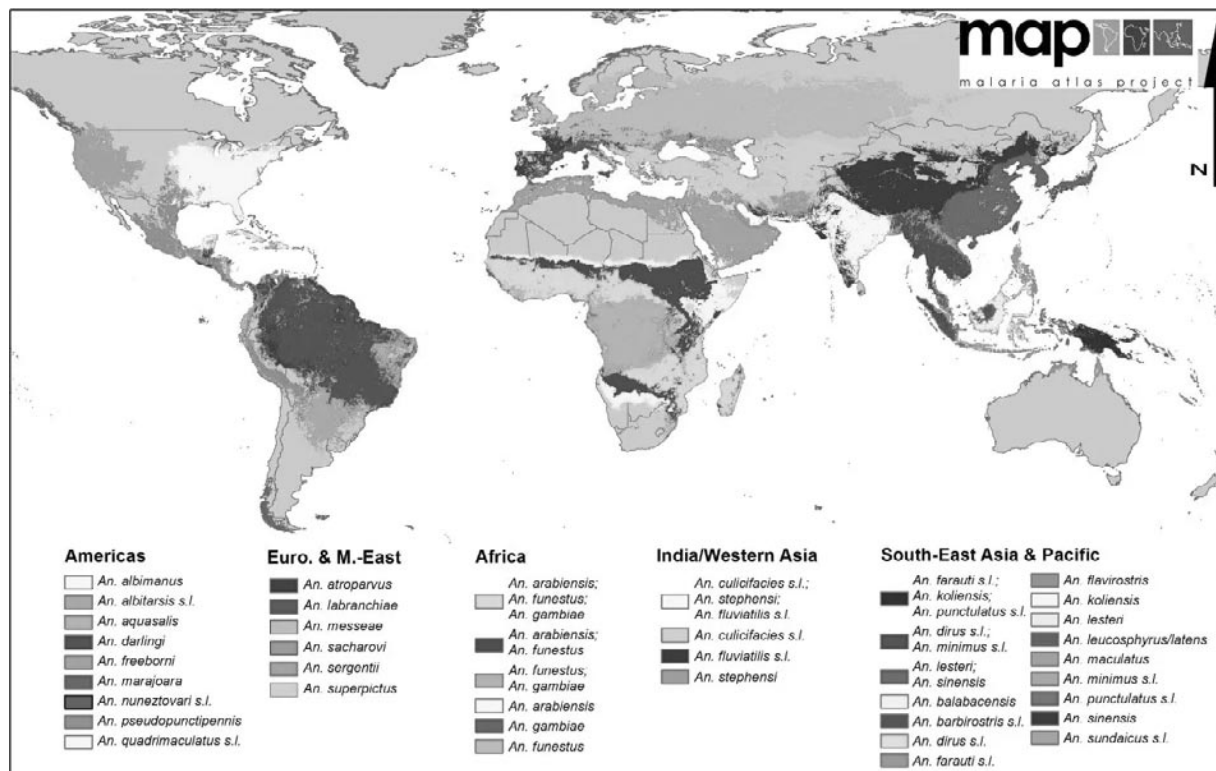


Figure 5 - Global distribution of dominant malaria vector species [2].

<http://www.parasitesandvectors.com/content/5/1/69>

It is estimated that climate change is going to have an impact on the malaria transmission especially in regions where temperate climate limits the presence of the vector, such as the highlands of Africa. Temperature influences several factors in the mosquito ecology such as the larval development time, the survival of larvae and adult mosquitoes, the duration of extrinsic period of the pathogen. Possible changes in the rain distribution and intensity throughout the year may also change breeding sites dynamic and persistence.

Human directly induced environmental changes such as deforestation and successive land use radically change the sun exposure and the local temperatures strongly impacting the *Anopheles* fauna composition. For example, *An. darlingi* in the Amazon region expanded its range and thereby increased the malaria risk. Deforestation increased the number of larval habitats as well as the breeding season, which results in a concentration of larvae in the forest fringe where shade, larval breeding sites and human blood meals are available close to each other.

Anopheles male and female mate in flight at dusk and stopped at full darkness. Males usually swarm above landscape markers such as bushes (but in some species such as *An. albimanus* males do not swarm). The virgin female enters the male swarm where the mating pair is formed in a very short time and then the couple exits the swarm to complete sperm passage. In successful mating events, male-female pair synchronizes their respective fundamental flight tones in a process called "harmonic convergence". Males of reproductively isolated sibling species of *An. gambiae*, fly in the same mating swarms, but rarely hybridize. The flight tone frequency matching occurs almost exclusively between males and females of the same molecular form, suggesting that this specific phenomenon play an important role in assortative mating. During mating, the male transfers a mix of seminal substances produced by the male accessory glands (MAGs) and known as "mating plug". The mating plug is composed by proteins, lipids and hormones which are digested by the females in a couple of days after mating. The most important physiological consequences of the mating plug transfer are that the female become refractory to other mating and egg development is started. *Anopheles* female is looking for blood during the night. In *An. gambiae* the female shows preference in feeding late at night and is considered to be endophagic and endophytic with differences related to "forms" (e.g. savannah or forest forms). In any case, *An. gambiae* is highly anthropophilic, with some opportunistic behaviour in host selection depending from the host availability. Vectorial capacity mainly depends on vector competence, female lifespan and host preference. Vector competence is determined by specific genetic traits under selective pressure by the *Plasmodium* parasite. Long lifespan allows to complete the extrinsic incubation period and, in the meantime, to perform several gonothrophic cycles. The marked anthropophily of the African vector species increases the probability to amplify the human to human cycle. The shape of these three main factors explains why more than 90% of the

world's malaria cases are in Africa. Of course, climatic conditions have a strong influence on the mosquito population density and seasonal dynamic, being close to optimal in most of the year in tropical regions.

VECTOR CONTROL

Malaria vector control targeting the larval stages was applied successfully against many species of *Anopheles* from the beginning of the 19th century. With the discovery of DDT in the 1940s, the approach was mainly devoted to indoor residual spraying (IRS), which was demonstrated to have stronger effectiveness on vectorial capacity than larval control [3]. However, it rapidly became evident that the “magic bullet” was not able to solve the problem and less ambitious integrated disease management approaches were developed under the WHO leadership (i.e. the Integrated Vector Management). From the analysis of past malaria control programs, it might be derived that environmental management measures are highly cost-effective in reducing malaria. Environmental management measures reducing larval development such as habitat modification, biological control and larviciding have been successfully used to control mosquitoes in many countries and these are recently becoming integral components of malaria control methods in Africa. When feasible, habitat modification such as drainage and elimination of large water bodies has the capacity to eliminate breeding sites in a permanent way, making this approach the most convenient.

Current beliefs retain that sustainable reductions of the entomological inoculation rate is possible when an integrated malaria control program with multiple well-coordinated interventions is implemented.

Vector control is still the main way to fight against malaria. WHO strategy in endemic countries suggests two main measures: the long-lasting insecticidal nets (LLINs) and the indoor residual spraying (IRS). To protect from malaria transmission LLINs must be deployed to achieve a high rate of covering and this is a main problem in poor regions where people cannot pay for them. It has been demonstrated that when the covering rate is maintained high during the whole transmission season, the incidence of malaria is reduced. A precise knowledge of local condition is fundamental in assuring the shaping of the most appropriate cost-effective malaria control program [1].

Recently, *P. vivax* malaria autochthonous cases have been registered for consecutive years in Southern Europe, requiring the immediate adoption of specific control measures focusing on the vector *An. sacharovi* [4].

INSECTICIDE RESISTANCE

The good results achieved in the reduction of malaria incidence are mainly due to vector control. Vector control is currently highly dependent on the use of pyrethroids, which are the only class of insecticides recommended by WHO to impregnate LLINs. As expected, resistance to pyrethroids has emerged in *Anopheles* in many countries posing new challenges on the future scenarios (Fig. 6).

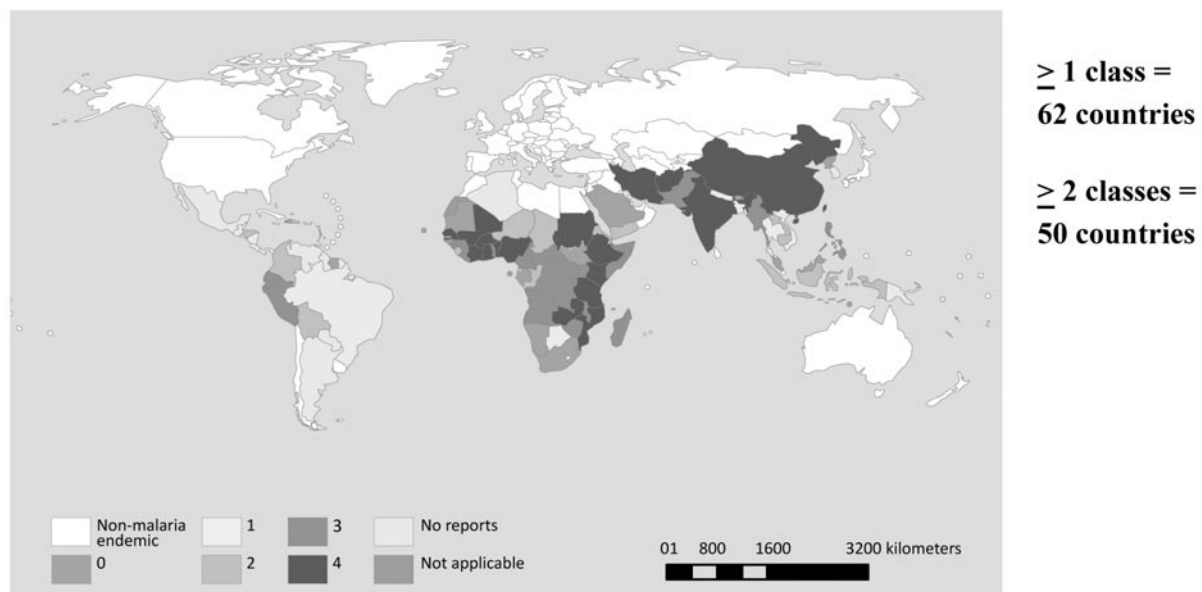


Figure 6 - Global status of insecticide resistance in malaria vectors 2010-2016 (from <http://www.who.int/malaria/publications/atoz/9789241514057/en/>)

Resistance to organochlorines, carbamates and organophosphates, used in IRS, is also a relevant problem. The best strategy to manage the resistance is based on the mixture of two insecticides with different mode of action in the treatment of net and the rotation of insecticides with different mode of action in IRS. Resistance to pyrethroid does not completely compromise the use of LLINs, which maintain good protection due to the mechanical mode of action. Likely no evidences of resistance to neonicotinoids have been produced so far.

Monitoring of insecticide resistance is an essential permanent component in national malaria control plans. There is large consensus that new insecticides and alternative tools are needed to sustain the battle against malaria. Several promising products are under evaluation.

SURVEILLANCE

Surveillance consists of spatial and temporal data collection supporting the most convenient organization of evidence-based data responses. In endemic countries surveillance systems are often not adequate in assessing the dynamic of the transmission, making more difficult to organize effective responses. Surveillance serves to call for resources and allocate them when and where needed, to assess the results of the programs, to early detect possible issues which may affect the future effectiveness of the program and to objectively evaluate the use of donations.

MALARIA ELIMINATION AND ERADICATION

Malaria elimination is defined as the interruption of local transmission in a defined geographical area, while malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of malaria infection. Interventions against malaria are no longer required once eradication has been achieved. Currently, WHO requires that a country is free from malaria for three consecutive years (without any autochthonous cases) to certify that it is free from malaria. In recent years, eight countries have been certified free from malaria by the WHO: United Arab Emirates (2007), Morocco (2010), Turkmenistan (2010), Armenia (2011), Maldives (2015), Sri Lanka (2016), Kyrgyzstan (2016) and Paraguay (2018).

GENE DRIVE AGAINST MALARIA

Gene drive technology seems to have the capacity to make available a method to eliminate malaria via the elimination or replacement of the vector species. Gene drive systems, such as those based on clustered regularly interspaced short palindromic repeats (CRISPR), have the potential to spread beneficial traits, such as sex unbalance producing males only offspring, in malaria mosquitoes (and also other vector species). This technology is raising ecological concerns that necessitate careful consideration prior to the deployment of the product in field condition. Testing plan in laboratory and confined semi-field condition are underway to explore all the possible risks associated with the technology. Progression through the testing pathway is based on fulfilment of safety and efficacy criteria, and is subject to regulatory and ethical approvals, as well as social acceptance [5].

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Malaria epidemiology, global impact and control strategies

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MALARIA

Malaria is a life-threatening infectious disease caused by the Plasmodium parasite. It is typically transmitted through the bite of infected female Anopheles mosquitoes. Across the world, five species of Plasmodium can spread human malaria and have been classified as follow: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*¹.

Transmission

Plasmodium is typically transmitted through the bites of infected female Anopheles and more rarely the transmission can be parenteral (blood transfusion) or congenital (mother to baby). The female mosquito needs to take blood meals for the production and maturation of its eggs.

There are approximately 430 different Anopheles species, but only 30-40 are competent vectors of malaria.

The activity of the mosquitos is mainly crepuscular and nocturnal. The mosquito is a heterothermic insect, able to survive only at temperatures above 15-18 °C with high humidity. For this reason, transmission also depends on climate conditions that can affect the survival and reproductive rate of mosquitoes, such as rainfall, temperature and humidity. In fact, in many places transmission is seasonal with a peak during or immediately after the rainy season.

Malaria epidemics can occur also when the climate or other conditions suddenly favor transmission in areas of low or absent immunity or when poorly immunized people, such as refugees and economic migrants, move into high transmission areas.

Human immunity is another important factor that can influence the transmission. In areas where malaria is highly endemic and transmitted throughout the year, older children and adults develop partial immunity and are at relatively low risk of contracting the severe form of the disease, while the most vulnerable groups include young children and pregnant women.

Clinical manifestation

The clinical manifestations of malaria depend on several factors such as parasite species, epidemiology, immunity and age.

After the infected bite, the incubation period varies generally from 7 to 30 days but may be much longer, depending on the immune status of the infected person, as well as the species of Plasmodium, the number of sporozoites, and the possible effects of chemoprophylaxis, with the shorter period observed in *P. falciparum* infection.

A longer incubation period is observed in *P. vivax* and *P. ovale*, which can produce dormant liver stage parasites, the hypnozoites. Hypnozoites can reactivate and cause malaria months after the initial exposure causing a relapse of blood-stage disease.

The evolution of the disease can be categorized into uncomplicated, complicated. Symptoms are usually common to all malaria species and are determined by the activation of the TNF-mediated cytokine cascade: they include fever, shivering, headache, arthralgia, gastrointestinal disorders (e.g. vomiting and diarrhea), anemia. Enlargement of the spleen and liver, mild jaundice, anemia, thrombocytopenia, elevation of bilirubin and increase in respiratory rate may occur.

P. falciparum is regarded as the most clinically significant infection due to an association with mortality and the intensity of infection in some regions of sub-Saharan Africa. Severe malaria occurs when the infection is able to cause serious organ failure. It is often characterized by hyperparasitemia, a condition which arises when over

¹ *P. knowlesi* is the latest parasite that has been discovered and it is currently confined to the Malaysia and Borneo regions, with few cases reported in Thailand, Vietnam, Myanmar, and Philippines. It is morphologically similar to *P. malariae*, but potentially severe as *P. falciparum*.

10% of red blood cells are infected with parasites. The major complications of severe malaria include cerebral malaria, pulmonary edema, acute renal failure, severe anemia, and/or bleeding. Acidosis and hypoglycemia are the most common metabolic complications. For the purposes of clinical management, therapeutic indications and prognosis, distinguishing between uncomplicated malaria, complicated malaria and non-*P. falciparum* species is essential.

Some groups in the population have a much higher risk than others of contracting malaria and being seriously ill: babies, children under 5 years, pregnant women, people living with HIV or AIDS, non-immune migrants, travelers.

EPIDEMIOLOGY

Currently around half of the world's population is at risk of contracting malaria.

In 2017, across the world, an estimated 219 million cases of malaria and 435 000 malaria-related deaths occurred. Children aged under 5 years are the most vulnerable, accounting the 61% of all malaria-related deaths. Approximately 70% of the world's malaria burden is concentrated in 11 countries (10 in the African continent, and India).

92% of malaria cases were reported in the WHO African Region, followed by the WHO South-East Asia Region with 5% of the cases and the WHO Eastern Mediterranean Region with 2%.

Five countries accounted for nearly half of the global malaria burden: Nigeria (25%), the Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%).

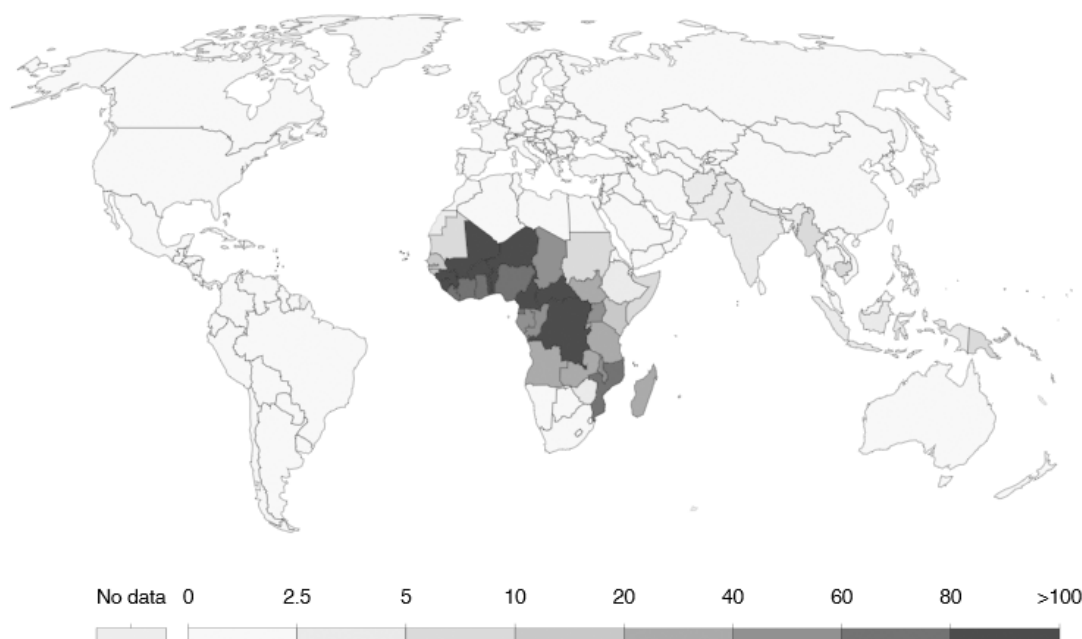
The WHO African Region also accounted for 93% of all malaria deaths in 2017 (Fig. 1) [1].

Malaria death rates, 2017

Age-standardized death rates from malaria, measured as the number of deaths per 100,000 individuals.

Age-standardization assumes a constant population age & structure to allow for comparisons between countries and with time without the effects of a changing age distribution within a population (e.g. aging).

Our World
in Data



Source: IHME, Global Burden of Disease (GBD)

OurWorldInData.org/malaria/ • CC BY

In 2017, *P. falciparum* was the most prevalent malaria parasite, accounting for 99.7% of estimated malaria cases in the WHO African Region, 71.9% in the Western Pacific, 69% in the Eastern Mediterranean, and 62.8% in the South-East Asia WHO Region.

Meanwhile, *P. vivax* was the predominant parasite in the WHO Region of the Americas, representing 74.1% of malaria cases.

Nonetheless, global efforts to fight malaria have led to a reduction of more than 500 million cases since 2000 in sub-Saharan Africa alone [2].

The incidence rate of malaria declined globally between 2010 and 2017, from 72 to 59 cases per 1000 population at risk. Despite an 18% reduction over the period, the number of cases per 1000 population at risk has not changed for the past 3 years [1].

CONTROL STRATEGIES

In May 2015, in order to address the global burden of malaria, the World Health Assembly adopted the WHO Global Technical Strategy for Malaria 2016-2030, in alignment with the Roll Back Malaria Partnership's Action and Investment to defeat Malaria 2016-2030 – for a malaria-free world. The Global Technical Strategy for Malaria 2016-2030 aims to guide and support countries in their efforts to achieve the strategic target of reducing global malaria incidence and mortality rates by at least 90% by 2030 [3].

In 2017, funding for malaria control and elimination was estimated at 3.1 billion USD). The government's contributions to endemic countries amount to 900 million USD, equivalent to 28% of funding requirements [3]. As a part of the vision of a world free of malaria, the strategy sets ambitious global targets for 2030, with milestones for measuring progress in 2020 and 2025 (Tab. 1).

Table 1 - Goals, milestones and targets for the global technical strategy for malaria 2016-2020 [3].

VISION – A WORLD FREE OF MALARIA			
GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

The strategy is built on three pillars:

1. Ensure universal access to malaria prevention, diagnosis and treatment;
2. Accelerate efforts towards elimination and attainment of malaria-free status;
3. Transform malaria surveillance into a core intervention.

Supported by two fundamental elements: harnessing innovation and expanding research, and strengthening the enabling environment.

ENSURE UNIVERSAL ACCESS TO MALARIA PREVENTION, DIAGNOSIS AND TREATMENT

The recommended interventions include vector control, chemoprevention, diagnostic testing and treatment.

Vector control

The most impactful broadly-applicable vector control measures are long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) (WHO 2013). In areas where the risk of malaria is high, it is essential to ensure that everyone is protected through the provision, use and timely replacement of LLINs or, where appropriate, the application of indoor residual spraying [3].

Even though this interventions continue to be effective in most areas, mosquito resistance to insecticides keeps being a critical concern: 60 countries have reported resistance to at least one of the four insecticides used in LLINs and IRS [4]. However, even when mosquitoes display resistance to the insecticide, people sleeping under LLINs have significantly lower rates of malaria infection than those who do not [5].

All countries need to develop and implement plans for monitoring and managing insecticide resistance, such as using insecticides with different modes of action through rotations between rounds of indoor residual spraying or multiple combined interventions [3].

Chemoprevention

Preventive treatment strategies are a key element to reduce transmission and mortality rates, depending on the intensity of malaria risk and the level of parasite's resistance.

WHO recommends intermittent preventive treatment for pregnant women, infants, and seasonal chemoprevention for children aged under 5 years [6]. Chemoprophylaxis is also indicated in non-immune individuals, such as travellers or migrants, who are more susceptible to malaria illness and death [3].

Diagnostic testing and treatment

Ensuring access to timely and adequate diagnostic testing and treatment in all settings is essential to reduce malaria morbidity and mortality. Everyone who is suspected to have malaria should have the diagnosis confirmed by effective parasite detection methods such as quality-assured microscopy or a rapid diagnostic test [3].

Universal access to WHO-recommended antimalarial medicines it should be ensured in order to prevent the development of severe illness and death. Patients with confirmed uncomplicated *P. falciparum* malaria should be treated with quality-assured artemisinin-based combination therapy. Instead, severe cases of malaria should be treated parenterally with artesunate or artemether [3].

The development of antimalarial drug resistance is one of the greatest threats to malaria control.

P. falciparum resistance to previous generations of drugs, such as chloroquine and sulfadoxine-pyrimethamine (SP), has spread in the 1950s and 1960s. The Greater Mekong Subregion, in South-East Asia, has long been the epicentre of *P. falciparum* resistance to artemisinin. In 2014, WHO launched an emergency operation in order to contain the spread of drug resistance [3;7].

The protection of the efficacy of artemisinin-based combination therapies is a top priority in order to avoid drug resistance [8]. The effectiveness of antimalarial drug should be regularly monitored to ensure early detection of drug resistance and take appropriate response measures when they occur.

The progression towards malaria-free status is a continuous process, and not a set of independent stages.

New hopes, the vaccine

Currently, there is no commercially available malaria vaccine. However, recent progress has been made with the trial of the RTS,S/AS01 vaccine against the most deadly form of human malaria, *P. falciparum*. In clinical trials, the vaccine prevented 4 out of 10 malaria cases in children who received all the four prescribed doses. The malaria vaccine was administered in 4 doses via intramuscular injection. During the phase 3 of RTS,S/AS01, conducted over the period 2009-2014, it reduced the number of malaria cases by half in children aged 5-17 months old. In 2019, a WHO-coordinated pilot programme started in Ghana, Kenya, and Malawi, delivering the vaccine through the routine national immunization programmes [9].

While it will be essential to find the best administration practice to improve the impact on child mortality and safety, malaria vaccine is expected to be an important tool used to eradicate malaria.

SURVEILLANCE AND ELIMINATION

Public health surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practices (WHO). Advances in information technology and communications offer prospects of increased timeliness of reporting, better sharing and analyses of data [3].

Effective surveillance must be guaranteed at all stages, up to the elimination of malaria.

Currently, many countries with a high incidence of malaria still have limited surveillance systems and are unable to monitor the impact of the disease. A stronger surveillance system that systematically collects, analyses and utilise health data for decision making is a corner stone of an effective public health system and is urgently needed to guarantee a rapid and effective response to prevent epidemics and outbreaks, monitoring impacts and progress.

Malaria elimination is the interruption of indigenous transmission of a specified malaria parasite species in a defined geographic area (reduction to zero incidence of indigenous cases), and continued measures are required to prevent the re-establishment of transmission. Malaria eradication is defined as the permanent reduction to zero of the incidence of malaria infection caused by all species of human malaria parasites, when eradication has been achieved, intervention measures are no longer needed (WHO).

Countries that have completed at least 3 consecutive years with zero cases of indigenous malaria can obtain WHO certification attesting to the elimination of malaria.

In recent years, great efforts and investments have been rewarded with the WHO certification of malaria elimination: United Arab Emirates (2007), Morocco (2010), Turkmenistan (2010), Armenia (2011), Maldives (2015), Sri Lanka (2016) and Kyrgyzstan (2016), Paraguay (2018), Uzbekistan (2018), Algeria (2019) and Argentina (2019) (Countries and territories certified malaria-free by WHO. WHO, 2019).

“Recent progress on malaria has shown us that,
with adequate investments and the right mix of strategies,
we can indeed make remarkable strides against this complicated enemy.
We will need strong political commitment to see this through, and expanded financing.
We should act with resolve, and remain focused on our shared goal:
to create a world in which no one dies of malaria.
I remain confident that if we act with urgency and determination,
we can beat this disease once and for all.”
Dr Margaret Chan

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Integrated control of helminthiasis: example from an endemic country

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The islands of Zanzibar, Unguja and Pemba, have been historically endemic for neglected tropical diseases, and particularly for urogenital schistosomiasis (UGS), soil-transmitted helminthiasis (STH) and lymphatic filariasis (LF). Zanzibar archipelago is part of the United Republic of Tanzania and lays a few degrees south of the Equator. Tropical climate, high population density, and soil contamination with human excreta, especially in rural area, determined the very high prevalence of helminthiasis. Moreover, the presence of *Culex quinquefasciatus* was responsible for the focal transmission of *Wuchereria bancrofti*, agent of LF. In early 80's morbidity due to these parasitosis was widespread, especially in children and women of child-bearing age, and this worrying scenario led the Ministry of Health (MoH) and concerted parties to start up control efforts. This paper describes the strategies that were put in place and the efforts undertaken in the last thirty years to control and eventually to eliminate some of these parasitic infections from Zanzibar.

Control of schistosomiasis: 1985-1990

The Schistosomiasis Control Programme started in Pemba Island in January 1986 with support from the World Health Organization (WHO) and the Italian Cooperation. The main objectives were to reduce micro-haematuria due to *S. haematobium* by 65% and visual haematuria by 90% in two years. The secondary aim was to progressively integrate control of other communicable and parasitic diseases (as LF, STH and possibly malaria) in the control strategy [1].

The strategy was based on community-wide selective treatments in the first year, and subsequently on selective periodic treatment of schoolchildren with single dose praziquantel (PZQ) given at 40 mg/kg body weight; health education of the community (radio, poster, meetings with teachers and community leaders) complemented the drug intervention [1].

The schistosomiasis control was successful and prompted to address other helminthic infections that were public health problems in Zanzibar and that could be controlled with a similar strategy.

However, the campaigns could not be conducted smoothly, as from 1995 to 2000 there was intermittent supplies of PZQ from WHO and African Development Bank (ADB), and in 1997 29 schools in Pemba had still a prevalence of schistosomiasis > 50%. Furthermore, hemastix were relatively expensive and not easily available. In order to overcome these constraints, a questionnaire-based approach was adopted to identify children with macro-haematuria. This method was validated comparing data obtained with the questionnaire and the results of urine filtration in 10 schools. Subsequently schools were ranked according to the questionnaires and those ones with more than 50% received selective PZQ (cost 1 US\$/tablet) treatment. When PZQ became cheaper (0,5 US \$) and hemastix more expensive (0,3 US \$), the schools with more than 50% prevalence received mass PZQ treatment according to the rank resulted from the questionnaire. The choice was driven by the cost-effectiveness of the intervention: 50% prevalence was the threshold, given those costs, as it was equal to screen everyone and treat the positive children, versus giving mass treatment without prior diagnosis to the whole school population.

Integration with control of other helminthic infection: 1990-2000

In late 80s' STH infections were perceived as a major public health problem in Zanzibar but there were no available data to confirm it. Between 1988 and 1991 parasitological surveys were carried out in the community and in schools to assess baseline health indicators, to better understand the geographical distribution of STH infections, to identify high risk groups, and to select the most cost-effective drug to be used in public health interventions [2].

The school survey revealed a very high prevalence of the three STH: *Ascaris lumbricoides* 79%, *Trichuris trichiura* 96 %, hookworms 94%, with 62% of the children suffering from triple infections. The epidemiological

study clarified two important elements: firstly it allowed to collect robust baseline data on prevalence, intensity, geographical distribution and age pattern of STH in Pemba island, and secondly evaluated the efficacy and safety of mebendazole 500 mg single dose to be adopted as drug of choice in the national helminth-control programme [2].

Data were also collected to assess nutritional and educational indicators. It was found out that 62% children were anaemic, (35% of iron-deficiency anaemia and 73% of severe anaemia were attributable to hookworm infections), 3,5% had severe anaemia, 45% children suffered from chronic malnutrition (stunted), and 5% children had acute malnutrition (wasted). Moreover, school attendance was studied as a mirror of children's health; the rate was approximately 70% (140/200 school days per child), taking into account all absenteeism problems [3].

In 1992 a randomized trial was undertaken to compare single doses 500 mg mebendazole and 400 mg albendazole against the three STH [4]. The study demonstrated similar efficacy of the two drugs to control STH and also showed that a generic mebendazole was as effective as the original product and it was ten times cheaper. The reinfection rates, however, were such that after 6 months intensities of infection were similar to pre-treatment levels. These findings suggested that deworming school children every four/six months was necessary. These data were essentials to guide the national control strategy and from 1994 to 2000 all school-children were regularly treated 2-3 times a year with single dose anthelmintics (mebendazole 500 mg or albendazole 400 mg) to control morbidity due to STH infections. In addition, once a year the children were also treated with a single dose of PZQ 40 mg/Kg.

School enrollment was around 75% and means were taken to outreach the non-enrolled children. Through an intensive media campaign before the school treatment, children non-enrolled were called in by their siblings and almost 60% of those children were reached by the deworming intervention in schools.

Monitoring and evaluation

Any control programme needs a monitoring and evaluation plan to assess the impact of the intervention. In Pemba Island the most important indicators were selected on the basis of timeline assessment. In the short-term, the indicators were: n. children treated (coverage), n. people cured and % worm burden reduced; the n. school days attended was also calculated. In the mid-term: n. of malnutrition cases prevented, n. of severe anaemia cases prevented, and the improvement of cognitive tests in schoolchildren was also assessed. For UGS, the morbidity was measured by testing micro and macro-haematuria and by the urinary tract pathology assessed by ultrasound. In the long-term: n. bladder cancer prevented (for UGS), n. school years gained, and the DALYs gained were planned to be evaluated.

Operational research showed that schistosomiasis control goals were reached in only two years: the prevalence dropped from 55.0% to 12% and the visual haematuria was reduced by 90% in 1989.

For STH infections, after one year the cure rates were 50%, 12% and 61%, and the reductions of the worm burden were 97%, 76% and 57% for *Ascaris*, *Trichuris* and hookworm infection, respectively [5]. Regarding nutritional indicators, deworming intervention reduced severe anaemia by 39%, significantly improved iron stores and growth of children (20% in weight and 7% in height). Iron and mebendazole had also a positive effect on motor and language development of pre-school children and periodic mebendazole treatment reduced wasting malnutrition in children. The blood loss prevented only by deworming 3 times/year was estimated to be about 250 ml, a quite significant amount. The school attendance was improved by 14% [3].

In 2000 the impact of periodic deworming on schistosomiasis was evaluated in an endemic village: visual haematuria dropped from 15% (1988) to 1.5%, severe infections (> 50 eggs/10 ml of urine) dropped from 18% (1988) to 8%, severe urinary pathology in adult males monitored by ultrasound was reduced from 40% (1988) to 19% [6].

The cost of deworming campaigns was also calculated, including cost of drugs, their distribution and the monitoring survey, and summed up to \$ 0.19 as yearly cost for a child treated with benzimidazoles three times/year. The cost per case of severe anemia averted was 15 US \$ and only 0,01 US \$ was the cost for any school-day gained/child.

Programme for the elimination of LF

Since the 70's LF was abundant in Zanzibar with focal transmission, and elephantiasis cases were visible and scattered both in Pemba and Unguja islands. Endemic foci were identified by previous surveys showing prevalence between 20% and up to 50% in Unguja, and between 10% to 15% in Pemba island.

Following the WHO recommendation to undertake LF elimination in any area with more than 1% prevalence, in 2001 Zanzibar started the Global Programme for Elimination of Lymphatic Filariasis (GPELF). The strategy was based on at least 6 yearly rounds of Mass Drug Administration (MDA) with ivermectin (6 mcg/kg) and albendazole 400 mg to the whole community, except pregnant and lactating women and children below 5 years of age. The other pillar of the GPELF was the management of LF morbidity, mitigating lymphedema and treating sick people with health practices to relief their morbidity burden. Hydrocele surgery camps were also successfully set up. The GPELF needed almost a military approach with a National Task Force that coordinated

an array of partners (pharmaceutical companies, International Agencies, WHO, local reference laboratories, local leaders, universities, and civil society). Ahead of the drug distribution an intense information and sensitization campaign was carried out in order to foster social mobilization to maximize coverage of MDA. Filaria prevention agents (FPA) were hired to distribute the drugs countrywide in 2 days. Adverse events were monitored, reported and appropriately managed [7]. The last MDA involved the administration of triple therapy with albendazole, ivermectin and praziquantel, and for the first time triple therapy was implemented in community campaigns and proved to be feasible and safe.

This strategy was successfully implemented with good drug coverage (average of >80% in 5 years) and led the prevalence of microfilariemia to drop to <1% in sentinel sites, a threshold for considering discontinuation of MDA campaigns for LF. Morbidity was also reduced by almost halving lymphedema and hydrocele patients. In addition, as side benefits of ivermectin treatment, there was a 60-98 % decline in scabies infections. Another subsequent study revealed that also infection by another neglected helminth, *Strongyloides stercoralis*, have been drastically reduced in Zanzibar due to the periodic use of ivermectin.

However, before declaring Zanzibar free from LF, a transmission assessment survey (TAS) after 6 years of MDA was carried out in 2012. School children in all four districts, aged between 6-8 years who were treatment-naïve were randomly selected for participation. Data showed that the prevalence of filaria antigen among this population was >1% for some sites in Unguja and >5% for some sites in Pemba. These results indicated that LF transmission had not halted and that MDA with ivermectin should have been re-introduced.

Elimination of UGS

In 2010 the MoH Zanzibar revised the strategy for control of STH and schistosomiasis, recommending increasing the frequency of PZQ delivery (from single annual to biannual). Furthermore, Zanzibar was selected by SCORE (Schistosomiasis Consortium for Operational Research and Evaluation) for trialing additional interventions, mollusciciding and behavioural change, for progressing towards elimination of schistosomiasis. An alliance was formed in 2012 including various partners (WHO Geneva, WHO AFRO, Schistosomiasis Control Initiative, Swiss Tropical and Public Health Institute, Natural History Museum - London, and Zanzibar Ministries) and was called the Zanzibar Elimination of Schistosomiasis Transmission (ZEST). The aim of ZEST was to assess the impact of three parallel control interventions in Pemba:- (i) The National Control Programme (NCP) alone based on PZQ treatment and health education, ii) NCP plus mollusciciding and iii) NCP plus behavioural modification. Fifteen Shehias (smallest administrative units) out of a total of 45 were randomized to each arm [8].

In addition, the National Institute of Parasitic Diseases, China, was interested to try out the model they have used to control/eliminate Asian schistosomes and to apply their expertise in the sub-saharan Africa setting. Zanzibar was selected among the pilot countries and substantial resources were allocated.

The SCORE project is just finished and its outcome is being analyzed. However, an interim analysis showed that prevalence dropped from 8% in Unguja and 15% in Pemba in 2011 to 3% in Unguja and 5% in Pemba in 2014, but with some persistent hotspots in which transmission was not halted.

Challenges and perspectives

From 2000 to 2006 Zanzibar was a perfect example of integrated control of helminthiasis. School children were treated every year with praziquantel plus albendazole or mebendazole and after 6 months ivermectin plus albendazole was delivered to the whole community. Health education on basic hygienic practices and on use and maintenance of latrines was given before any deworming campaign. Latrines were built in schools by UNICEF, and safe water supplies were developed both in schools and in villages with support from UNDP and ADB. PZQ and benzimidazoles were available in peripheral health centres.

However, despite almost three decades of control efforts, prevalence of STH is nowadays still high, and UGS and LF are yet to be eliminated.

Several challenges have to be identified and addressed.

-) After many years of treatment, community fatigue was perceived and the compliance of MDA has to be sustained.

-) A solid surveillance system for LF and eventually UGS should be built. Efforts must be focused on the identified hot spots of schistosomiasis transmission, and intensively foster integrated control (WASH, vector control) for the elimination of transmission.

-) Drug efficacy of benzimidazoles and PZQ must be monitored in the area with high drug pressure, and combination of anthelmintics, especially against the persistent worm *T. trichiura*, should be tested.

-) Finally, helminth control must be kept sustainable through better integration. Teachers and drug distributors demand incentives and MDA activities are not cheap. Although deworming medicines are so far available through donation from drug companies, their cost of distribution and monitoring should be sustained by local MoH and communities, without depending on external support.

A concerted effort should be made by the MoH and partners for a final push to eliminate helminthiasis as public health problems in Zanzibar.

Figure 1 - Summary of helminth control in Pemba

	1986-1988	1989 -1993	1994-1998	1999-2002	2003	2004	2005	2006	2007	2008	2009-2011	2012-2013	2014-2017
Praziquantel (PZQ)	1	2	3	4		6		7			9	10	11
Mebendazole (MBZ)			3								8		
ALB + Ivermectin (IVM)						5		7					12
Albendazole (ALB)							6				9	10	11

1	Selective chemotherapy to children and adults - test and treat campaign, twice a year
2	School targeted treatment, twice a year
3	Zanzibar Helminth Control Programme (ZHCP) initiated PZQ for school targeted treatment, only in high prevalence schools MBZ for school targeted treatment, twice a year
4	Irregular distribution ☐ school selective or targeted treatment depending on prevalence, according to the rank
5	GPELF: Community MDA (> 5 years of age), once a year. In 2006 PZQ was also included in the package and the three drugs were delivered together in the communities in MDA (7). ZHCP, > 5 years of age, once a year
6	2004 - 2005, Community MDA in Pemba (supported by SCI - Schistosomiasis Control Initiative) 2006, School based treatment in both Islands
7	Integrated Triple Drug Administration (ALB+IVM+PZQ), Community MDA, only once
8	Preschool targeted treatment (12 - 59 months), twice a year, supported by UNICEF
9	School targeted treatment, once a year: (The treatment was partially implemented), no PZQ distributed
10	School targeted treatment, once a year
11	School targeted treatment followed by MDA twice /year
12	ALB+IVM reintroduced after the TAS

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Antibiotic resistance. Global overview and global control strategies

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GLOBAL BURDEN OF ANTIBIOTIC RESISTANCE

Antimicrobial resistance (AMR) - i.e. the ability of microbes to evolve and render our antimicrobial drugs ineffective - is a major challenge of the modern medicine. The emergence and dissemination of AMR threatens to undermine nearly a century of medical advances, causing a heavy human and economic cost. Overall, it has been estimated that on a global scale AMR could cause 10 million deaths per year, and a reduction of 2% to 3.5% in Gross Domestic Product by 2050. The emerging resistance to treatments is affecting all spheres of communicable diseases, including the 'Big Three' HIV/AIDS, Tuberculosis and Malaria, but infections due to antibiotic-resistant bacteria remain a major concern worldwide.

In 2015, in the EU and European Economic Area (EEA) eight antibiotic-resistant bacterial species caused an estimated 671 689 infections, of which 63.5% occurred in hospitals and other health-care settings [1]. Overall, they accounted for an estimated 33 110 attributable deaths and 874 541 disability-adjusted life-years (DALYs), being third-generation cephalosporin-resistant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA) the leading causative agents overall. In the United States, AMR organisms cause more than 2 million infections and are associated with approximately 23 000 deaths each year [2].

In low- and middle-income countries (LMICs), information about the excess morbidity and mortality caused by multidrug-resistant (MDR) bacterial infection are often inconsistent, because of insufficient data integration, inadequate laboratory quality and poor microbiological diagnostic facilities. In LMICs, the burden of antibiotic-resistance is exacerbated by low socio-sanitary conditions, poor health facilities, inadequate legislation and monitoring systems on the use of antimicrobials, as well as by the lack of programs for AMR prevention and control. A systematic review of published studies on antibiotic susceptibility from West Africa, evidenced a widespread resistance, at moderate to high levels, to commonly used antibiotics for bloodstream and/or urinary tract infections, such as ampicillin, cotrimoxazole, gentamicin and amoxicillin/clavulanate, and the emergence of third-generation cephalosporin resistance [3]. In India, *E. coli* isolated from the community showed high overall resistance to ampicillin, nalidixic acid, and cotrimoxazole (75%, 73%, and 59%, respectively), and almost one in three isolates resulted resistant to gentamicin. Moreover, from 2008 to 2013, *E. coli* resistance to third-generation cephalosporins, fluoroquinolones and carbapenems increased from 70% to 83%, from 78% to 85%, and from 10% to 13%, respectively. High rates of MRSA in clinical isolates from various Indian studies have been documented, with levels as high as 54.8% (ranging between 32% and 80%) [4].

In Bolivia, very high resistance rates to old antibiotic and an alarming increasing trends of resistance to newer drugs have been documented both in commensal bacteria and in clinical isolates, at the community level and in hospital settings, through 30-years of surveillance activities, carried out in the Chaco region [5].

FACTORS ASSOCIATED WITH ANTIBIOTIC RESISTANCE

The rapid bacterial replication cycle offers the opportunity for genetic mutation, allowing the emergence of genetic variants that contribute to withstand the effects of antibiotics. External pressure, produced by antibiotic exposure, triggers resistant strains selection. Then, dissemination of resistance determinants can occur by clonal expansion or mobilization of plasmids, i.e. circular DNA segments, encoding genetic factors for antibiotic resistance, which are able to move from one bacterial species to another via conjugation. Therefore, any antibiotic use, even appropriate and conservative, can contribute to the development of resistance, while unnecessary and excessive consumption enhances this phenomenon and acts as a major driver of resistance

dissemination worldwide. Between 2000 and 2015 global antibiotic consumption, expressed in defined daily doses (DDDs), increased by 65%, (from 21.1 to 34.8 billion DDDs), while the antibiotic consumption rate increased 39% (from 11.3 to 15.7 DDDs per 1,000 inhabitants per day) [6]. However, the increase in global consumption followed different patterns in high-income countries (HICs) and LMICs. Whereas antibiotic use in HICs increased modestly, the consumption in LMICs is rapidly growing, along with rising incomes, affordable antimicrobials, in the absence of stewardship and other control programs. India, China, and Pakistan, which are LMICs leading consumers, increased their antibiotic DDDs in the period 2000-2015 by 103%, 69%, 75%, respectively [6].

Overuse and misuse of antimicrobials are influenced in many countries by their availability over the counter and without prescription. Non-prescription use occurred worldwide, ranging by countries from 19% to 100%, but it is especially common in LMICs [7]. Non-prescription drugs are mostly purchased at a pharmacy, or obtained from friends, family, or home. Contributing factors for non-prescription antibiotic supply were poor national regulations, limited availability of qualified pharmacists, commercial pressure on pharmacy staff, consumer demand, inappropriate prescribing practices and lack of awareness of AMR.

In recent years, consumption of newer and last-resort antibiotic classes, such as glycyclines, oxazolidinones, carbapenems, and polymyxins, rapidly increased, with far higher rates in HICs in comparison with LMICs [6]. Interestingly, unexpected high rates of carriage of resistant determinants to last-resort antibiotics, e.g. colistin, have been reported also in rural populations from LMICs, where their use is occasional and limited to referral urban hospitals [8]. In this perspective, the large non-human usage of antimicrobials in veterinary medicine and animal husbandry may play a crucial role, as additional source of AMR. Antibiotics, including compounds of critical importance for human medicine, are widely used for disease prevention and growth promotion in food-producing animals. In the United States, antibiotic use in livestock production represents 80% of total antibiotic consumption. A conservative estimate of the global antibiotics consumption in livestock in 2010 was 63 151 tons, but the trend is likely to rise, driven by the growth in consumer demand for animal proteins and the expansion of large-scale intensive farms in middle-income countries [9]. Antimicrobial agents are essential for treating and controlling infectious diseases in animals. However, in large-scale intensive farming systems, growth-promoting and prophylactic antimicrobials are routinely administered in sub-therapeutic doses, creating ideal conditions for the emergence and the selection of resistant bacteria in animals. Harmful resistance genes can spread from the animal reservoir to humans through the environment (waterways and soils, contaminated by animal waste) and the food products, and with the professional exposure of agriculture workers, by direct contact.

GLOBAL CONTROL STRATEGIES

In 2015, the World Health Organization (WHO), in a tripartite alliance with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE), issued a Global Action Plan, based on five priority objectives: (i) to improve awareness and understanding of antimicrobial resistance through effective communication, education and training; (ii) to strengthen the knowledge and evidence base through surveillance and research; (iii) to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; (iv) to optimize the use of antimicrobial medicines in human and animal health; (v) to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions [10].

Antibiotic stewardship programs, based on restrictive practices (e.g. prescription authorization) or persuasive practices (e.g. postprescription review with feedback) have been increasingly implemented in several hospitals around the world (mostly in the HICs), aiming to tackle antibiotic misuse and overuse, to improve patient outcomes, and decrease adverse drug events, including antibiotic resistance selection.

The promotion of hygiene measures in health-care settings is essential to pursue infection prevention and control. For instance, hand washing campaigns are a low-cost, straightforward intervention, which demonstrated the power to drastically reduce the transmission of health care-associated pathogens, i.e. the major source of antibiotic resistant micro-organisms.

The use of antimicrobial agents in animals need to be controlled and reduced, to contain antimicrobial resistance emergence in livestock production. The OIE promotes the development and the harmonisation of national antimicrobial resistance surveillance and monitoring programs, in food-producing animals and in products of animal origin for human consumption. Moreover, the antimicrobial exposure in animal husbandry should be monitored, including the quantities and the usage patterns of antimicrobial agents by animal species, antimicrobial type and class, route of administration and type of use. Responsible and prudent use of antimicrobials, in accordance with the marketing authorisation, is warranted, and it should take into account the importance of some agents in human and veterinary medicine. For instance, animal use of fluoroquinolones, third/fourth generation cephalosporins and colistin (listed in the WHO category of Highest Priority Critically Important Antimicrobials) should be urgently prohibited as growth promoters and preventive treatment by all

countries, and their prescription in veterinary medicine should be limited to microbiologically-documented infections, with no alternatives available.

More research is needed to address knowledge gaps about the potential impact of antimicrobials in the environment and the associated risks for human health. The impact of interventions to prevent or remove this environmental contamination should be monitored, to understand the effectiveness of existing practices for waste management and water processing, as well as investigating novel methods and strategies. For instance, the response to environmental contamination by AMR pathogens could include prevention strategies (e.g., pre-treating sewage from elevated sources, like hospitals, before release) and removal strategies (e.g., wastewater treatment processes).

In conclusion, AMR is emerging as a shared global challenge, embracing numerous sectors beyond human health. An effective “One Health” approach, based on a whole-of-society engagement, with the coordination among all relevant stakeholders, within animal health, agriculture, food security and economic development, is urgently needed [10].

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HIV/AIDS in Africa

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INTRODUCTION

The first AIDS cases were described in 1981. The knowledge of the natural history of HIV, of the diagnosis, of the treatment and prevention has enormously advanced since then. The progresses in the past years have made it possible to face HIV not as a death sentence anymore, but as a chronic and treatable disease.

Although the phylogenetic history of HIV originates from Africa, the explosion of HIV epidemic in low-income countries, particularly in Sub-Saharan Africa, was recognized only at the beginning of the '90s. At that point, the epidemic had already caused a severe demographic crisis in many countries of southern Africa.

In several settings where the access to medical care is not fully guaranteed, the possibility to diagnose and treat HIV is particularly difficult and, together with economic difficulties, social and political concerns continue to hamper progress in HIV care.

The costs of the first licensed antiretroviral drugs (combined antiretroviral therapy - cART) were unaffordable by African patients but also by the majority of their governments. For this reason, the access to new molecules in the African continent has been delayed by at least 10 years, causing an excess of AIDS mortality, otherwise preventable.

In 2000, a big legal trial took place in Pretoria, South Africa, involving many of the pharmaceutical companies who produced antiretroviral drugs. Thanks to this trial, the molecules still covered by patent were able to be formulated as equivalent drugs, and consequently they became cheaper, allowing their purchase where it was not possible previously.

Finally, the epidemiology of HIV infection, the diagnostic tools and the therapeutic strategy are in continuous evolution, also in low-income countries. Therefore, it's possible to assume that, in future years, the scenario of HIV in Africa will resemble more and more to those achieved in high-income countries.

These promising advances have led the World Health Organization (WHO) to propose a plan to eliminate the HIV/AIDS from our planet or at least, more likely, to make this disease no longer a public health issue.

EPIDEMIOLOGY

The last report on HIV epidemic [1] estimates that in Sub Saharan Africa 25.7 million people are living with HIV and 660,000 individuals died from this plague in 2017 [1].

WHO recognizes two main regions in Sub Saharan Africa: "eastern and southern Africa" and "western and central Africa" which include countries with similarities in geographical and economic features. The former accounts for the 53% of PLHIV (people living with HIV) in the world whereas the latter accounts for a lower percentage.

Western and central Africa includes some of the poorest countries worldwide and this explains why this region has difficulties to progress in HIV care as promoted by the WHO.

Despite a stable decline in the number of HIV diagnosis, Sub Saharan Africa accounts for 66% out 5,000 new infection contracted every day in the world [1,2].

AIDS-related mortality declined by 42% from 2010 to 2017 in eastern and southern Africa, reflecting the rapid pace of treatment scale-up in that region. In western and central Africa, the decline was lower (24% reduction) as a consequence of a different access to HIV care in the two regions.

Mortality reduction remains higher among women than men. This gender gap is particularly high in sub-Saharan Africa, where 56% of people living with HIV are women. In 2017, an estimated 300,000 men in sub-Saharan Africa died of AIDS-related illness compared to 270 000 women.

This reflects how relevant early diagnosis and higher treatment coverage (mainly during pregnancy) among women is. In 2017, an estimated 75% of men living with HIV in eastern and southern Africa knew their HIV

status, compared to 83% of women living with HIV of the same age.

Moreover, the highest number of children with HIV worldwide lives in Sub-Saharan Africa. In 2017, 1,110,000 PLHIV aged under 15 were reported, 160,000 of whom were newly diagnosed and in the last year 82,000 children died because of AIDS.

As regards HIV acquisition in Sub-Saharan Africa, most of PLHIV declared heterosexual intercourses. The remaining cases were represented by men who have sex with men (6-12%), sex workers (2%) and people who inject drugs (1-10%).

A small rate of mother-to-child HIV transmission still persists despite a stable decline in the last years.

In eastern and southern Africa, 81% of PLHIV knows his HIV status; 66% is on antiretroviral treatment and 52% has an undetectable HIV viral load.

In western and central Africa, the corresponding rates are dramatically lower: 48%, 40% and 22% respectively.

Despite these figures, WHO still believes in the dream of achieving the 90-90-90 goal (90% PLHIV diagnosed, 90% on therapy and 90% viro-suppressed) by 2030 [1].

HIV CARE AND CLINICAL MANIFESTATION

WHO guidelines recommend an integrated model of HIV care, to be improved by linking health services between the rural areas and reference centers [3].

Community-based HIV testing services have been widely implemented in some African countries. This is an important approach to reach people who seldom use clinical services and facilitates early diagnosis as well. As a part of this integrated model, screening tests might be offered in community sites such as community-based organizations, schools, workplaces, religious institutions and mobile services. It is mandatory to offer HIV testing in all settings, to people of all ages and particularly in case of symptoms suggesting advanced disease [4].

Only people with a positive reactive test will be referred to a central health-care facility.

In the last years, WHO recommended a task-shifting in the health sector and now specifically recommends that trained and supervised *lay providers* (people without a formal professional or paraprofessional certificate) can independently conduct safe and effective HIV testing and related educational programs both in the community and in health facilities [3,4].

Interestingly, HIV self-testing represents a new approach for people who may be unable or reluctant to attend existing HIV test services as well as to people who frequently retest. The use of HIV rapid diagnostic tests (RDTs, ELISA) at the point of care has become an important strategy to expand access, allowing results in 1 hour and enabling immediate linkage [4].

Additional assays, such as the Western blot, are needed to confirm the diagnosis and are usually performed in referral centers where cART can be provided [4].

People with a non-reactive HIV test who report recent risky behavior should be advised to return in 4 weeks to repeat testing. If they test HIV negative after 4 weeks, only individuals with ongoing risk behavior should be advised to perform an HIV test every 6-12 months. Moreover, it is recommended to provide for high risk populations other preventive measures such as PEP (post-exposure prophylaxis), PrEP (pre-exposure prophylaxis) and circumcision [4].

Pregnant women have to be tested and, in case of a negative result during the first trimester, it is recommended to repeat the test before delivery [4].

In all cases, the counseling before and after the HIV test is considered as a key moment in HIV preventive care [4].

A reactive HIV test should be confirmed by a second, different test and possibly performed at a site where enrolment in care and cART prescription could be offered, if indicated [4].

If the diagnosis of HIV infection is established, a health care provider has to carefully explain the meaning of being HIV positive, the treatment benefit and the importance of a regular follow up.

Other key elements of post-test counseling are information about prevention of HIV transmission, support to facilitate partner and family disclosure and psychological help [4].

In addition, an integrated HIV care includes [4]:

- Decentralization of cART distribution or support in the transfer to HIV care center;
- Prevention, screening and treatment of hepatitis B and C, STI (sexual transmitted infections), tuberculosis and other opportunistic infections, when suspected;
- Vaccination (their effectiveness is enhanced when CD4⁺ cell count >200/μl);
- Sexual and nutritional education;
- Psychological support and assessment of suicide risk;
- Prevention, screening and treatment of non-communicable diseases

The main goals of the aforementioned WHO recommendations are to create a close relationship between the patient and the health care providers to better involve the subject in care and consequently, to fight against the *loss to follow up* phenomenon [4].

As concerns the clinical manifestations, HIV-related symptoms vary according to the infection stage.

WHO defined 4 clinical stages for adults, excluding the acute infection phase or flu like syndrome [5]:

- Stage 1: asymptomatic patient or with persistent and generalized lymphadenopathy
- Stage 2: moderate unexplained weight loss (<10% of presumed or measured body weight), recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis), Herpes zoster, angular cheilitis, recurrent oral ulceration, papular pruritic eruption, fungal nail infections and seborrheic dermatitis;
- Stage 3: unexplained severe weight loss (>10% of presumed or measured body weight), unexplained chronic diarrhea for longer than 1 month, unexplained persistent fever, persistent oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis, severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia), acute necrotizing ulcerative stomatitis, gingivitis or periodontitis and unexplained anaemia, neutropaenia and/or chronic thrombocytopaenia.
- Stage 4: HIV wasting syndrome, *Pneumocystis jiroveci* pneumonia, recurrent severe bacterial pneumonia, chronic herpes simplex infection, oesophageal candidiasis extrapulmonary tuberculosis, Kaposi sarcoma, cytomegalovirus localized infection, toxoplasmosis of the brain HIV encephalopathy, extrapulmonary cryptococcosis, disseminated nontuberculous mycobacterial infection, progressive multifocal leukoencephalopathy, chronic cryptosporidiosis and isosporiasis, disseminated mycosis, cerebral or B-cell non-Hodgkin lymphomas, symptomatic HIV-associated nephropathy or cardiomyopathy, recurrent septicemia, invasive cervical carcinoma or atypical disseminated leishmaniasis.

This classification slightly differs among children (available at <https://www.who.int/hiv/pub/arv/arv-2016/en/>).

In comparison with other HIV staging models, the advantage of WHO classification relies on an easier application in settings where CD4+ T-cell count is not available.

AIDS status is defined by stage 3 or 4 manifestation or by CD4+ T-cells < 350/μl. Besides that, in resource-limited settings, without advanced lab exams and/or imaging, the staging only relies on clinical presentations and physical examinations.

In order to prevent opportunistic infections, WHO recommends prophylaxis with sulfamethoxazole-trimethoprim for adults (including pregnant women) with advanced HIV clinical stage (stage 3 or 4) and/or with a CD4+ T-cell count ≤350 cells/μl and in patients with tuberculosis (irrespective with CD4+ cells count). Additionally, sulfamethoxazole-trimethoprim shows a wide spectrum of action also against bacteria, fungi and parasites [3].

ANTIRETROVIRAL THERAPY

At present, the available antiretroviral drugs are not able to eradicate the virus but they succeeded in the control of the viral replication. A sustained and stable viral suppression allows the functional recovery of the immunity system, and consequently a reduction of HIV-related comorbidities, a significant decline of HIV transmission improving dramatically the patients' quality of life.

Nowadays, this goal is possible both in high-income and in low-income countries thanks to highly effective cART.

Since 2016, WHO has recommended the "treat-all" strategy removing all limitations on eligibility for cART among PLHIV. All patients are eligible for treatment, including children and pregnant women, irrespectively to the clinical stage or CD4+ T-cell count. However, WHO estimates that in Africa only 60% of PLHIV has access to cART [3].

Therefore, in resource-limited settings, it is commonly accepted to prioritize HIV infection at stage 3 or 4, adults with CD4+ cells count <350/μl, children and pregnant or breastfeeding women [3].

The cART prescription generally follows a careful clinical examination to exclude opportunistic infections and to evaluate the immune status [3,6].

cART is a lifelong therapy and its efficacy depends on a full adherence of patients. For that reason, health-care workers are recommended to explain carefully the cART rules at baseline: expected benefits, possible side effects, dosage, day schedule. The risks of a low adherence to cART are key factors to illustrate.

Initiation of ART should always consider nutritional status, comorbidities and other medications being taken to avoid possible interactions, to identify possible contraindications and to evaluate dose adjustments. Moreover, patients should be informed about the possible reactions to cART initiation, that mainly appear in the first three months: unknown allergies and, above all, the paradoxical appearance of opportunistic infections or other symptoms consistent with IRIS (immune reconstitution inflammatory syndrome) [3].

When starting cART, it usually takes time to collect these clinical data and sometimes cART is prescribed elsewhere from the site where the diagnosis was established.

By contrast, many studies conducted in Africa in recent years are showing the benefits of the *same-day/accelerated ART initiation* but nowadays, none of the international guidelines are recommending this strategy as a first choice.

However, accelerated cART initiation is justified in case of acute infections or due to any barrier to the normal procedure.

Table 1 shows the first line cART regimens [3]. Usually, in addition to these guidelines, national recommendations on cART are published in each Country [6].

After cART initiation, WHO recommends to monitor, when possible, CD4+ cells count every 6 months and viral load at 6 and at 12 months.

In settings where the viral load measure is not available, treatment failure should be suspected according to clinical signs or because of persistently low CD4+ cells counts.

Table 1 - First-line ART regimens for adults, pregnant or breastfeeding women, adolescents and children [3].

	Preferred first-line regimens	Alternative first-line regimens ^a
Adults	TDF ^b + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG ^d TDF + 3TC (or FTC) + EFV400 ^{c,e} TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG ^{c,d} TDF (or ABC) + 3TC (or FTC) + EFV400 ^{c,d,e} TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP
^a ABC or boosted protease inhibitors (ATV/r, DRV/r, LPV/r) can be used in special circumstances. ^b Monitor renal function, if feasible ^c Safety and efficacy data on the use of DTG and EFV400 in pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available. ^d Conditional recommendation, moderate-quality evidence ^e EFV at lower dose (400 mg/day). 3TC lamivudine, ABC abacavir, AZT zidovudine, DRV darunavir, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, TDF tenofovir.		

CONCLUSIONS

In Africa, as in high-income countries, HIV/AIDS is a treatable condition, even if not definitively curable. It means that our main goal is now to create the cultural basis and the health care facilities to face HIV infection as a chronic condition as in high-income countries.

Several barriers still need to be overcome in the near future: reducing the costs of cART, which are still too high for the poorest countries, tackling stigma and discrimination with greater effort, extending access to HIV testing, treatment and prevention in settings with the highest burden of HIV infection.

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Ultrasonography in the diagnosis of parasitic diseases in resource-limited settings

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Ultrasound (US) is a safe, versatile, and cost-effective imaging modality. Its use in the field of infectious diseases and its impact on clinical management in low-resource settings (reviewed in [1] and [2]) are well documented. The WHO have long acknowledged that it should be available worldwide to assist the clinician in the diagnostic process [3]. Recent technological advances with progressive reductions in cost and size of US machines coupled with significant improvements in imaging quality that have increased availability and clinician usage in low-resource settings. In industrialized countries US is used in conjunction with more expensive non-portable imaging techniques (CT, MRI), but in many low resource settings US and X ray together can meet over 90% of the imaging needs [2]. As a screening tool, ultrasound has great utility for many tropical diseases. Because it is non-invasive, portable, and in expert hands can be done rapidly it is the perfect tool for both population based and treatment studies.

In this chapter, we briefly review the use of ultrasound in the evaluation of tropical parasitic diseases in resource-limited settings. We describe the utility of US in the context of each disease and describe the common signs detectable by US on abdominal US. Chest US, where most clinical research is currently been done, is not included in the chapter because of space constraints.

GENERAL PRINCIPLES

Due to the property of sound waves, ultrasound imaging is at its best when examining fluid filled structures and solid organs. The heart, gallbladder and bladder all image well because of the fluid filled nature of these organs. The liver, kidney, and the spleen image extremely well due to their size, location and their ultrasonographic properties. As a result, infectious diseases that affect the liver and spleen are particularly amenable to ultrasound imaging. Many of the diseases that have been best described involve the liver and the spleen.

PARASITIC DISEASES

Amebiasis

Ultrasound imaging is the first-line imaging modality used to diagnose liver abscesses, and guides staging, localization, and monitoring of treatment response. Specific sonographic features depend on the stage of disease. US alone cannot reliably differentiate pyogenic from Amebic Liver Abscesses (ALA), however it does facilitate real-time interventional procedures such as Percutaneous Drainage (PD). The presence of anchovy-paste on aspiration or drainage is indicative of the amebic nature of the fluid collection. US is also valuable in assessing the prevalence of subclinical ALA in endemic areas, thus providing important epidemiological information on this condition.

Schistosomiasis

Schistosoma is a water borne helminth that mainly affects the Genitourinary (GU) and Gastrointestinal (GI) Tract. The most important species in terms of prevalence and morbidity are *S. mansoni*, *S. hematobium* and *S. japonicum*. In the acute invasive stage of the disease non-specific hepatosplenomegaly and enlarged perihilar lymph nodes may be seen by US. In chronic schistosomiasis, the primary morbidity is caused by fibrosis around

schistosomal eggs that fail to escape their human host. These eggs become trapped in the bladder, GI tract and portal system, and the resulting fibrosis and its subsequent effects can be detected by US.

Liver alterations detectable by US in chronic infection by *S. mansoni* are due to this granulomatous reaction to schistosomal eggs acting as foreign bodies. Liver findings on ultrasound demonstrate various degrees of periportal fibrosis (Symmers' fibrosis). The degree and character of fibrosis can be quantified and graded. Correlation between the severity of the liver fibrosis on ultrasound and severity of disease has been demonstrated in small studies.

In advanced stages of *S. mansoni* infection where a retracted liver is associated with portal vein dilation, US can easily detect portal hypertension, congestive splenomegaly, gastro-esophageal varices and typical gallbladder wall thickening.

Chronic infection with *S. haematobium* is characterized by granulomas in the bladder wall, causing wall thickening and intravesical bleeding, and may be complicated by bladder cancer that are easily detectable with US. Ureters and kidneys can eventually be involved as well with resulting hydronephrosis, hydroureter, culminating in renal failure.

In community-based surveys of *S. haematobium*, US detectable pathology was found to be more common in children than adults and was correlated with intensity and prevalence of infection. In a number of longitudinal studies, US has been used to examine the resolution of uropathy following chemotherapy. Most patients investigated showed a high rate of improvement.

US plays an increasingly important role in determining re-treatment intervals, based on the recurrence of morbidity. It has also been used to examine the resolution of hepatic and urinary lesions following chemotherapy for *S. mansoni* and *S. haematobium*.

Cystic echinococcosis

Cystic echinococcosis (CE) is the parasitic condition that has most benefited from the introduction of US in clinical practice and epidemiological studies. US has enabled noninvasive population screenings and evaluation of disease in community based studies. US has proven to be invaluable for the success of control programs for CE in endemic areas.

A re-arrangement of a previous classification by Gharbi and colleagues in 1981 was issued in 2003 by the WHO-IWGE (Informal Working Group on Echinococcosis). This classification divides the cysts into three relevant groups according to their biological activity: active (CE1, uniloculated, and CE2, with daughter cysts), transitional (CE3) and inactive (CE4 and CE5, solid content with calcifications) (Fig. 1). CE3 transitional cysts were later differentiated into CE3a (with detached endocyst) and CE3b (active, predominantly solid with daughter cysts) as they respond differently to non-surgical approaches. CE1 and CE3a are early stages, and CE4 and CE5 are late stages.

This classification is crucial as a stage-specific approach remains the best tool currently available to guide rational treatment choices for hepatic CE, including minimally invasive percutaneous treatments.

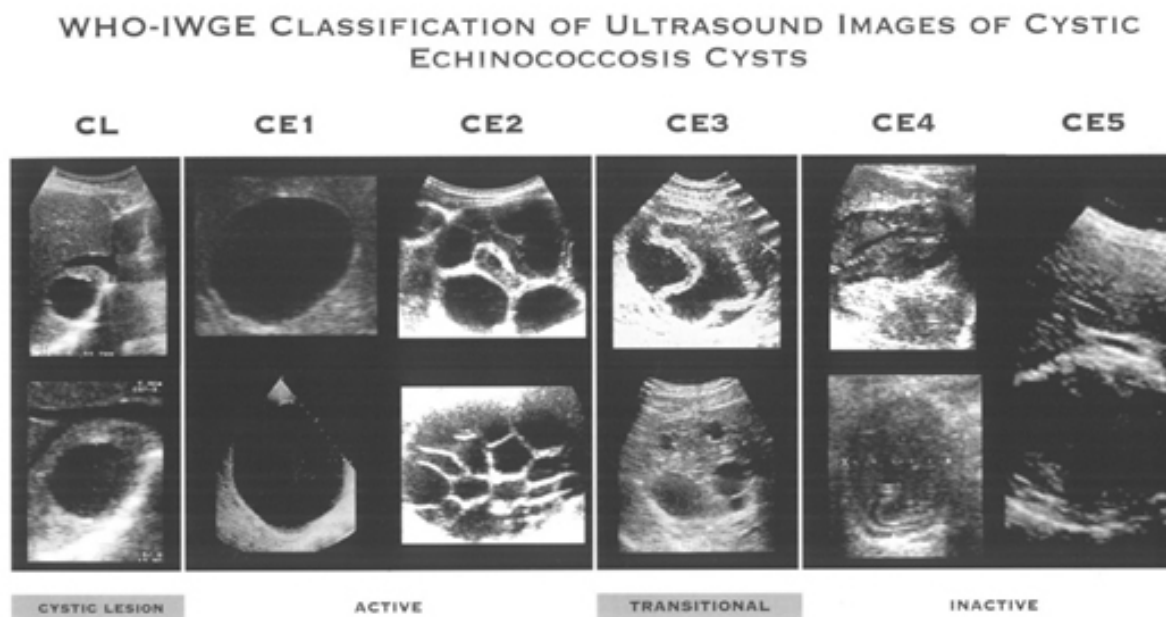


Figure 1 - WHO-IWGE classification of ultrasound images of cystic echinococcosis cysts

Fascioliasis

In the liver of patients with fascioliasis, small necrotic lesions form along the migratory paths of juvenile flukes. These can be seen as hypoechoic small lesions, which do not coalesce and are typically arranged along serpiginous tracts, from the surface of the organ to deep within the hepatic parenchyma [4]. They can change in quantity and location over time. This particular lesion arrangement can be helpful in the differential diagnosis of tumors, pyogenic abscesses and visceral larva migrans [5].

In the chronic stage, adult flukes are seen inside the biliary ducts as a few centimetres in length with single or multiple elongated filamentous echoic structures. Spontaneous movement may be observed. Other ultrasound findings include thickening of extra-hepatic bile ducts, common bile duct dilation, cholelithiasis, small calcifications of the liverparenchyma, liver abscesses, hepato-splenomegaly, gallbladder wall thickening and ascites [5].

Clonorchiasis and Opisthorchiasis

In general US is helpful in evaluating the sequelae of parasite infestation rather than visualizing the parasite itself. Flukes or aggregates of eggs are occasionally seen as non-shadowing echogenic foci or casts within the bile ducts.

Ultrasound findings include diffuse intrahepatic bile duct dilatation, truncation and increased periductal echogenicity. Other secondary infectious complications, such as pyogenic cholangitis, liver abscesses, stones, pancreatitis and cholangiocarcinoma, can also be seen.

Recent studies have addressed sonographic abnormalities [6] and changes in sonographic findings in *O. viverrini* after treatment in highly endemic areas [7]. Prevalence and severity of US changes have recently been described in endemic areas such as Laos [8].

Filariasis

Beginning in the late 1980s US of the scrotal area in men with Lymphatic Filariasis (LF) was used to evaluate prevalence and stage of “filaricele” (a term including all conditions related to LF infection). The term “filaricele” encompasses hydrocele (fluid collection between the layers of the tunica vaginalis), chylocele (presence of echo-dense fluid with floating particles, at risk of testicular necrosis), lymphocele (dilation of suprastesticular lymphatic vessels) or lymphoscrotum (thickened scrotal skin, porous and wart-like, pain attacks, leakage of lymph fluid)

US can provide important diagnostic and risk-stratification information. It is valuable in guiding both therapeutic options and monitoring responses to antifilarial treatments. Using color power Doppler and pulsed wave Doppler one can visualize a worm “nest” in dilated lymphatic vessels and the worms’ typical movement pattern called “filarial dance sign (FDS)” (Fig. 2). Although primarily used to monitor LF in the scrotal region of men infected with *W. bancrofti*, US has also been successfully used to detect FDS and lymphatic pathology in women and in pathology caused by *B. malayi*, where worm nests are less stable over time.

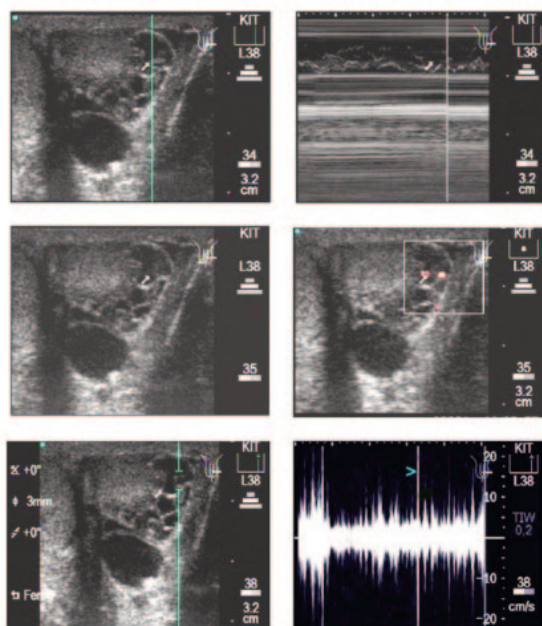


Figure 2 - Filarial dance sign

Longitudinal scan of the left testis of a patient with filariasis.

Upper left: In para-testicular position an enlarged lymphatic vessel with one or more adult worms is seen. (arrow) The vertical line signals the cursor position of the M-mode seen on the upper right of the figure. Middle left: same worm nest as seen above. Middle right: The Color Doppler-mode shows that this worm's nest contains much free lymphatic fluid, which induces a signal due to worm movements in the worm's nest.

Lower left: The same worm nest as above. Lower right: In the PWD mode the filarial dance sign is seen as an undulating band as a function of time.

(From: Mand S et al: Animated documentation of the filarial dance sign (FDS) in bancroftian filariasis. Filaria J, 2003)

Onchocerciasis

US may complement physical examination in patients with onchocerciasis, as it is able to detect a proportion of non-palpable nodules [9] and to differentiate onchocercomas from other lesions (e.g. lymph nodes, lipomas). It has also been used to assess the efficacy of antifilarial treatment in clinical trials.

Moving worms are only detectable in nodules with cystic areas, where parasites appear as an acoustic enhancement reflected from tissue moving in hypoechoic areas of the nodule, whilst living worms are not detectable in more compact onchocercomas. *O. volvulus* movements are rare and slower compared to filariae in the lymphatics.

Ascariasis

US is a highly sensitive and specific non-invasive method for the detection of helminths in the biliary tract. Diagnosis of biliary ascariasis requires a high index of suspicion because the worms move freely in and out of the biliary tract and therefore can be missed on biliary imaging. In longitudinal sections, adult *A. lumbricoides* have an echogenic non-shadowing tubular structure with a hypo- or anechoic centre, and can be seen moving with a slow-waving pattern. Multiple worms in the bile duct produce a spaghetti-like image, with alternating echogenic and anechoic strips or if densely packed in the bile duct, can appear as a hyperechoic pseudotumor. US can also detect *A. lumbricoides* worms in the small bowel.

CONCLUSION

Ultrasound is a potent tool for diagnosis, screening and monitoring of treatment response for a wide range of infectious diseases, including parasitic infestations. The utility of US is greatly amplified by its accessibility in low resource settings, where other imaging modalities may not be available. The range of application of US in infectious disease is broad and still expanding as small portable US scanners are increasingly available and their price is decreasing. Clinicians, particularly those working in low-resource settings, need to be trained in ultrasound either as a general diagnostic tool or as limited, point-of-care aid to clinical management. Protocols for US scanning for specific parasitic diseases [10] should be adopted by specialists and non-specialists alike.

Ultrasound has many documented and emerging benefits for the diagnosis and management of parasitic diseases. An effort to document new evidence and formalize scanning protocols coupled with a drive to increase access and training to US, will help deliver these benefits to the patient bedside in low-resource settings.

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Safe water for all

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The issue of water and sanitation was the theme of several United Nations Conferences which, through resolutions, determined the international approach to the management and the right to water. During the Conference on Sustainable Development, Rio+20, held in 2012 in Rio de Janeiro, sustainable water management was considered fundamental for food security, nutrition and sustainable agriculture.

The Rio+20 Declaration recognizes water as the center of sustainable development and emphasizes that in order to eradicate poverty, empower women and protect human health, it is necessary to guarantee access to safe drinking water for all and to integrate water management at all levels, through resource mobilization, capacity building and technology transfer, particularly in countries with limited resources. It is also crucial to reduce the loss of biodiversity that affects the water supply and health of people around the world [1].

Water security is defined by the United Nations as the ability to provide the population with sustainable access to adequate quantities of quality water, acceptable to human wellbeing and socio-economic development, in order to ensure protection against water pollution and disasters and preserving ecosystems in a climate of peace and political stability, while safely managed drinking water is defined as use of an improved drinking water source that is located on premises, available when needed and free from fecal and priority chemical contamination [2].

In 2015, 17 Sustainable Development Goals (SDGs) were defined with the aim of developing a coherent and universal plan of action for man, natural systems, the planet and development, to be implemented by all countries. The definition of SDG 6 "Ensure availability and sustainable management of water and sanitation for all" is a key objective for Agenda 2030 and the motivation for the progress of many other SDGs, including health, education, city sustainability, gender equality, etc.

Water, sanitation (intended as the provision of facilities and services for the disposal of human urine and feces) and hygiene are the key points of SDG 6 [3]. These three aspects are summarized internationally by the acronym WASH and mean all measures to reduce the exposure of people to diseases through an integrated assessment and management of contributing factors for water contamination.

The safe management of WASH services is not yet widespread in the poorest areas of the world. As reported by UNICEF, in 2016 "892 million people worldwide still practiced open defecation, 2.3 billion people still lacked even a basic sanitation service and 844 million people either used improved sources with water collection times exceeding 30 minutes (limited services), unprotected wells and springs (unimproved sources), or took water directly from surface water sources" [2].

It is known that safe water for all is essential for long-term sustainable development, however, most definitions of "safe water" are imprecise. At the domestic level, water security is generally defined as "access of all people to sufficient quantities of safe water" [4], as safe water is thought to be free of microorganisms, chemicals or radiological contaminants that constitute a threat for health and for a healthy and productive life.

The consumption of non-drinking water leads to a large number of diseases due to microbiological contaminations caused by bacteria, viruses, protozoa and helminths that cause gastrointestinal diseases such as diarrhea, scabies, cholera and hepatitis. At the same time, the lack of sewage treatment should not be neglected, which in addition to producing an unpleasant environment contaminates the soil, surface water and groundwater. A further element to consider related to safe water is solid waste management and disposal. Indeed, target 6.3 of SDG 6 itself asserts: by 2030, improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals and materials.

Municipal waste disposal into landfills is still the primary option in several countries. Furthermore, ISWA [5] notes that in many developing economies, uncontrolled open dumpsites are more widely employed than controlled and engineered landfills.

It has to be considered that contamination of groundwater and surface water in urban areas in low-income countries with organic, inorganic and microbial pollutants due to leachate is a common and significant problem. Leachate is the liquid generated after landfilling, since solid waste undergoes physico-chemical and biological

changes. In particular, as the result of precipitation, surface runoff and infiltration or intrusion of groundwater percolating through landfill storage, the degradation of the organic fraction of the wastes in combination with percolating rainwater leads to the generation of a highly contaminated liquid called leachate.

The various chemical compounds in landfill leachate can lead to significant damages in ecological systems, food chains and ultimately human population. These effects can range from toxicity to carcinogenicity.

Obviously, the risk for groundwater contamination and, as a consequence, for human health, in the case of dumpsites is much higher than engineered landfills which have waterproof liner at the bottom. As consequence, existing studies examined the groundwater contamination and the health risk posed by leachate from dumpsites [6].

With this in mind, a recent publication [6] proposed a model, using well consolidated equations and assumption, taking into account the path the pollutant makes to reach the water table and the point of exposure, to easily identify the boundaries of the area of risk related to the presence of a dumpsite, beyond which a local community may use or build a safe well for drinking water.

Further attention must be given on emerging contaminants (ECs), many of which are used every day by humans, such as pharmaceuticals, steroid hormones, and illicit drugs, or are found in widely used products such as personal care products (PCPs), surfactants and plasticizers [7]. Recent progress in analytical chemistry has made it possible to detect a growing number of ECs in surface water and several studies have shown their presence in rivers and lakes, both in Industrialised and Developing Countries [8,7].

It has to be considered that residues of these contaminants are usually collected in wastewater after their consumption and due to their low removal in wastewater treatment plants (WWTPs), these compounds enter freshwater ecosystems. In several cases where WWTPs are not existing (in particular in Low Income Countries), these substances enter the aqueous environment directly [8].

It should be clear to ensure the safe provision of water for all, it is important to work following a holistic approach to prevent environmental damage and health risks, starting with the protection of water resources in order to ensure the protection of health with special attention to risks related to exposure, use and consumption of water. In this context, the Water Safety Plans (WSPs) and Sanitation Safety Plans (SSPs) are useful tools for the risk prevention and mitigation in water supply [9] and in the sanitation [10] systems.

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The art of decision in Tropical Medicine. Some notions of decision analysis applied to medical examples in Tropical Countries

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PREFACE

Both in clinical medicine and in public health, doctors make decisions every day. In many circumstances decisions have to be made under uncertainty. The theory of medical decision-making, largely based on clinical epidemiology and decision analysis, is not a new one: it has been applied so far to complex medical problems of general interest, mainly in the context of developed countries. The purpose of this short text is different: we would like to make the principles of clinical epidemiology and decision analysis available to the Tropical Doctor, who so often suffers from limitation of resources, in order to help him to make better decisions in his daily practice.

Most of this text deals with applications to the individual, clinical medicine, but we are convinced that the same principles may be helpfully applied to public health, too. As we should never forget, public health ultimately affects individuals, not simply numbers, and we believe that the two “worlds” should be strictly linked.

When a new patient presents to a consultation with a problem, what we intuitively do is to mentally elaborate a list of diagnostic hypotheses to explain his major complains.

This initial process is of key importance, and our intuition may be wrong if we immediately look for the “*most common*” causes, as we normally tend to do. We should rather give priority to the “*serious and treatable*” causes, regardless their frequency, in order to be sure not to miss them.

Then we start looking for “*arguments*”, either to confirm or to exclude our hypotheses; not all arguments have the same “power” (or “strength”): an essential component of the “medical art” is to look for “stronger” arguments, for any given hypothesis.

Sooner or later, this diagnostic work will come to an endpoint; that is, we will have to take a decision. In most circumstances, the final decision, for any given hypothesis in our “diagnostic panorama”, will be either to treat the patient or to exclude the hypothesis.

Sometimes we reach the certainty of a given diagnosis, or (on the contrary) we are able to reject the initial hypothesis: of course, there is no need for any decision strategy in such clear-cut situations! But often we have to take decisions under a variable degree of uncertainty: if we consider that we have reached a sufficient level of *probability of disease*, then we will treat, otherwise we will not. We call this minimum acceptable level of probability, or of certainty, the *decision threshold*.

Sometimes the decision is a bit more complex. Suppose that at the end of the diagnostic process we are still doubtful, and we have the option to do a “last test”, which is unfortunately hazardous, and/or very costly, and/or hardly available (as is so often the case in tropical countries!).

In this case, the decision to do or not to do the test should also be considered. There are two thresholds: the *action threshold* (either to treat without test or to do the test) and, at the opposite end, the *exclusion threshold* (either to do the test to or exclude without test).

We will discuss in depth the factors influencing all these key elements of the decisional process through the analysis of real cases. We will also show the underlining mathematical basis, but through a simplified model which should be easy to understand and apply by any Tropical Doctor in his daily work.

At least, we hope so...

I– THE DECISION THRESHOLD

Introduction

It is quite easy to find in medical textbooks the differential diagnosis of different clinical pictures, as well as the relevant tests and the treatment indications for each suspected disease. The real challenge for a doctor is not really to have this theoretical knowledge, but rather to know when he should confirm or reject a hypothesis, communicate the diagnosis of a serious disease, prescribe a very expensive or dangerous treatment, decide general prophylactic measures for a potential outbreak of an infectious disease.

If we are absolutely sure that a patient has a given disease, the decision to treat him is easily made, unless the treatment itself is potentially more dangerous than the disease (such as DEC for loiasis), or unaffordable (such as may still be the case with protease inhibitors for some African patients with HIV); on the other end, if we are sure that he has not that disease, we will rule it out and concentrate on other possible explanations of his clinical presentation. But in real life we are frequently faced with incertitude, and we have to take decisions on a probability basis: the main problem is to establish, for any given disease, a probability threshold in order to decide if a medical treatment, or any other medical action is warranted or not. Very complex mathematical formulas are available to calculate those thresholds [1]. Our purpose is rather to define the threshold notion and discuss the main factors affecting its value.

The decision threshold

The probability for a patient to suffer from a given disease varies from 0% to 100%. At the end of the clinical consultation, when we will have exhausted all the available diagnostic arguments in order to confirm or refute that given hypothesis, we will have to take a decision: either we will undertake an action (generally a treatment, but also the communication of the diagnosis of an untreatable disease), or we will conclude that we do not have enough evidence. What probability of disease do I need to decide to undertake a medical action? Let's start with an example:

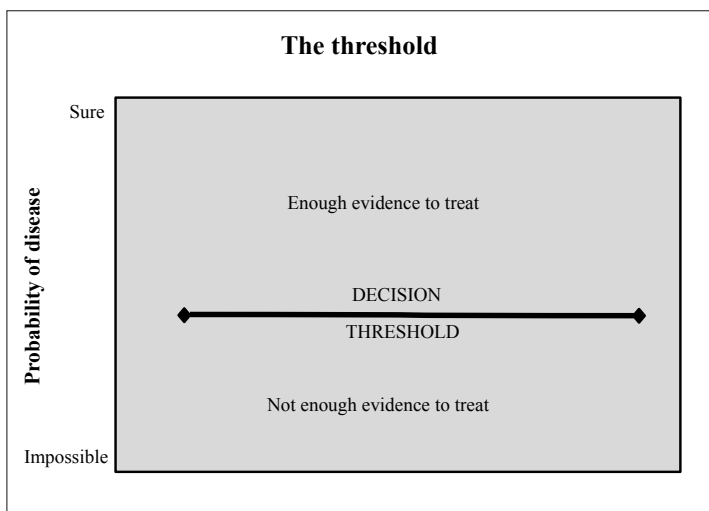
*In Nigeria a 30-year-old man presents with fever and pain in the right upper quadrant. He is not jaundiced, the urine is normal coloured. The thick film reveals very scanty *P. falciparum* trophozoites (but we are in an endemic zone). The chest x-ray is normal. The WBC count reveals leucocytosis (14.000/ml). The ESR is 55; the stool exam is negative for amoeba trophozoites.*

The doctor suspects a liver abscess, but an ecography is not available, nor a serologic test. Has he got enough evidence to treat, anyway, for *E. histolytica*? Should he rather treat for malaria and "wait and see"?

A girl from Peru has been coughing for the last two months. She has an irregular low-grade fever. She has lost 3 kg in the same period, the ESR is 50, and the formula is unaltered. Three serial sputum exams are negative. A x-ray is not available.

What should the doctor do? Is he authorised to start a TB treatment despite the negative sputum?

The probability needed to decide whatever medical action might be called decision threshold.



The higher it is set (towards 100%), the more we take the risk to erroneously leave a significant number of affected patients without treatment (**false negative**): this is particularly dangerous when the disease is very serious and/or contagious (i.e., a meningitis), when a medical and/or surgical treatment would be life-saving (a typhoid fever with bowel perforation), or when the consequences could affect the community (epilepsy in a bus driver).

The lower it is set (towards 0%), the more we take the risk to unnecessarily treat a significant number of patients without the disease (**false positive**): not only this is particularly dangerous when the treatment itself is very toxic (such as Melarsoprol for *T. gambiense*), or very long and expensive (TB), or when the diagnosis

itself may imply a social stigma (AIDS or leprosy, for instance): but also because it may delay the right diagnosis (and treatment) of the true cause of this patient's picture.

How to estimate a decision threshold?

We said that a threshold could be expressed as a **probability** level: if we set a threshold at 80%, it means that we need to be at least 80% sure that the patient has the disease in order to decide to treat. If we had a hypothetical

population of 100 patients presenting like him, it would mean that 80 of them have the disease and would be correctly treated, while the remaining 20 do not have the disease and would unnecessarily receive the treatment (**false positive**, as we said): it is easier to estimate a threshold if we put it like that: **“How many patients would I accept to treat unnecessarily”?**

Let's take typhoid fever as an example: the antibiotic treatment is very effective, somehow expensive, with little toxicity: on the other hand, the disease is very serious and its complications are life-threatening; there is no social stigma, and the risk for the community is low. I suppose you would agree, provided that the antibiotics are available, to treat up to 8 or 9 people without the disease, rather than living one or two patients with typhoid without a treatment: if it is the case, then your decision threshold for a typhoid fever is between 10 and 20%.

Attention! If your threshold for typhoid is set at 10%, it does not necessarily mean that only 10 in 100 cases that you treat are really typhoid cases! In many cases you will be able to reach a higher degree of certitude, in others you will be able to rule out the hypothesis almost completely. It would be obviously better to reach a higher degree of certainty, whenever possible, in order to reduce the risk of an unnecessary treatment! **But when all the available arguments (tests) have been exhausted, if the diagnosis is still doubtful, then the decision to treat or not will necessarily rely on the threshold.**

A threshold is in fact as simple as a balance between the relative risks and costs of the two final options we are faced with at the end of the diagnostic process: to treat this patient for this disease (and accept the risk inherent to an unnecessary treatment) or to leave him untreated (and accept the risk of the disease consequences).

Factors influencing the decision threshold

Several factors affect the choice of the necessary degree of certitude, or probability, to make a decision. We will examine the most important ones and analyse their influence on the threshold.

1. The objective factors: the disease and the treatment

They are doubtless the key factors affecting the decision threshold. We could define this threshold as the **balance** between the risk of the disease for the affected patients who would remain untreated (**false negative**), and the untoward effects of the treatment (in the largest sense) for those unaffected who would be unnecessarily treated (**false positive**). Most other factors act on the threshold by influencing, in one way or another, these two key factors.

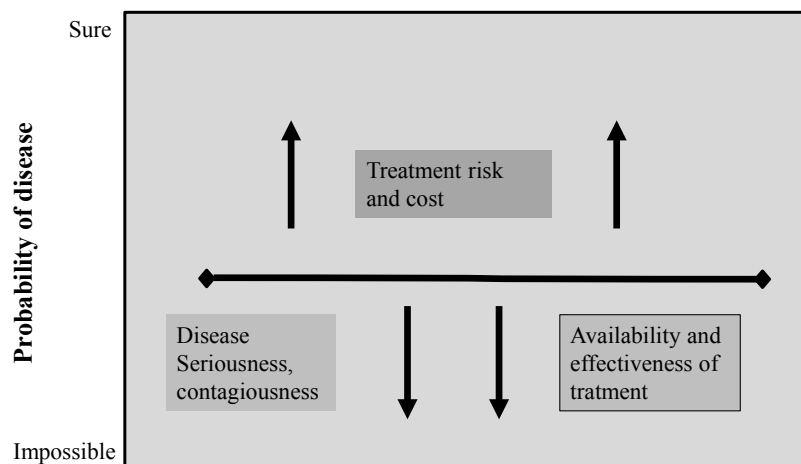
The disease

- **the seriousness of the disease:** the more serious the disease, the lower we will put the decision threshold in order to minimise the number of “**false negative**”, that is, patients with the disease but left untreated.
- **the contagiousness:** a serious AND contagious disease will have a lower threshold, as it is intuitive: a TB patient is personally at serious risk to die if left untreated, as it is a patient with sarcoidosis; but the former disease implies also a risk to the community which, as it is intuitive, will further lower its threshold.

The treatment

- Is an **effective and safe treatment** available? This will lower the decision threshold for two reasons: first, we will try to leave as few patients as possible (**false negative**) without a potential benefit; secondly, we will not care so much of the consequences of the treatment for the not affected people who would be

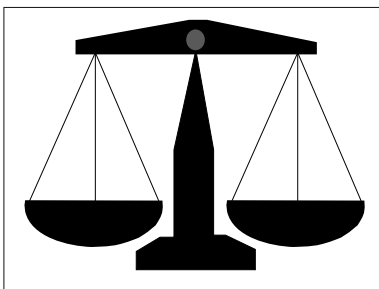
Factor influencing the threshold



unnecessarily treated (**false positive**), as the treatment wouldn't do any harm (a good example could be an antibiotic treatment in the suspicion of a bacterial meningitis). On the other hand, a treatment which is of little if any utility (such as is nifurtimox for advanced American trypanosomiasis), and/or very dangerous (such as melarsoprol for neuromeningeal *T. gambiense*) will move the threshold upward, for opposite reasons.

- **The cost of the treatment.** This is a key factor, perhaps the most important one influencing the threshold in a country with limited resources. The decision threshold for most diseases is higher in poor countries, compared with rich, Western countries, precisely for the cost factor, directly influencing availability. The cost obviously moves the threshold upward. If a treatment is very expensive, we will treat a patient only if we are "reasonably sure" that he has the disease. We could not afford to treat many "false negative" with a high cost for them or for the community, depending on the payment system. A good example is the antimonial treatment for visceral leishmaniasis, which we will analyse in some detail later.

The threshold: a balance between the option to treat and the option to give no treatment:



Not surprisingly, the consequences of a serious disease left untreated are generally much more serious than the undesired effects of the treatment, then the decision threshold for most serious diseases is usually low [2-4].

The general factors

They depend on the context, and they are probably those factors which most contribute to the difference between the "rich" medicine of Western countries and the medicine in countries suffering from scarcity of resources. The general factors mainly act by influencing some of the objective factors that we have just examined.

- The economical context: this is by and large the most important general factor, which directly affects the availability and cost of the treatment. Therefore, generally speaking, we can state that decision thresholds for the same diseases tend to be higher in poor countries.
- The health facilities: strictly influenced by the economical context, they directly affect, in the widest sense, the availability of an effective and safe treatment. A splenectomy is not as safe in a rural, African hospital as in a referral, Western hospital with intensive care facilities: therefore the threshold for a splenectomy (under the suspicion of a ruptured spleen, for instance, or of a splenic abscess), will be higher in the rural hospital.
- The social and cultural context. A hysterectomy under the suspicion of a cervical cancer would be much less acceptable in a context where the fertility is a recognised factor of social consideration, and therefore its threshold will be generally higher in Africa than in Europe.
- The political context. In emergency medicine (war, disasters, epidemics...) the aim is to save as many lives as possible in a short time, and therefore the threshold of elective surgeries, for instance, will be very high if compared with a "normal", stable political situation!

2 The subjective factors

They may affect both the patient and the doctor and are hardly quantifiable. The modern clinical epidemiology studies with increasing depth these factors, especially on the patient's side, in order to take into account his own expectancies and points of view. The key message here is a simple but frequently neglected one: at any time a difficult decision has to be made with your patient, please speak with him, inform him, discuss with him the alternative outcomes!

A clinical example

A 12-year-old boy is taken to the hospital because of a pain at the right lower abdominal quadrant. He has vomited twice. At the physical exam the abdomen is tender, and a Blumberg is frankly positive; the WBC count is 18.000, with shift to the left. He is immediately referred to the surgeon for appendicitis.

What is the decision threshold for appendicitis? The untreated disease may evolve to peritonitis with a fatal outcome; the surgical treatment is a routine for an expert surgeon and the risk is very low. The "weight" of the disease in the balance is therefore much higher, and the threshold is very low: I would prefer to unnecessarily refer 7 children to the surgeon rather than missing three cases of appendicitis, then I would set my threshold not higher than 20%. In reality, in many cases (as in our example) the probability reached is intuitively much higher than that! Many cases are treated at a high level of suspicion, and the probability to treat a "false positive" is low; in many other cases, the initial suspicion is readily ruled out. But there is a subgroup of cases where the clinical picture is not clear-cut and the laboratory is not definitely helpful.

The key message of a low threshold is the following: if I am not able to rule out the suspicion of a very serious disease I'd better treat it, even though I think that the probability is low.

The tests and the threshold

Does the availability of diagnostic tests influence the threshold? Intuitively most of us would answer yes: if you have better tests, you can set the threshold at a higher level. This is wrong. The decision threshold is basically a balance between the disease and the treatment factors: the diagnostic tests (arguments) are rather the tools we use to move upward or downward on the probability scale (see next chapters). We can say that, if we have good tests, we will often be able to reach a higher degree of certainty. In a poorer context, with limited diagnostic facilities, we will often decide under conditions of incertitude (that is, near the threshold).

Conclusion

The main purpose of the clinical work is not necessarily to reach a diagnostic certitude, but rather to take the best decision with our patients. We have just analysed in a qualitative way the main criteria affecting the decision threshold. But as we said, a threshold is a probability, therefore there must be a way to calculate, at least with some approximation, its value!

As a matter of fact, the threshold can be formally calculated, based on rather complex formulas. This goes well beyond the scope of this chapter, for three main reasons: first, the application of formal calculations (part of what is generally referred to as decision analysis) is generally reserved to complex medical problems of special interest, while our purpose is to apply the logic of decision to the daily medical practice (where there is no room for higher mathematics...); second, it has been repeatedly observed that a thorough analysis of the qualitative criteria allows a good estimate of the decision threshold; third, we need criteria to assess the actual probability of disease of a given patient, which we will learn in the following chapters. Therefore, once we will have analysed the properties of the arguments and tests, we will go back to the thresholds in order to show their mathematical basis in a simple way.

II - THE POWER OF AN ARGUMENT

Introduction

When a patient presents with a complain, we spontaneously elaborate a list of hypotheses compatible with the clinical picture, then we start looking for arguments in favour or against each hypotheses (or in other words, to confirm or refute the diagnostic suspicion). Intuitively, not all arguments have the same "power": some of them are strong, some are less strong, and some are definitely weak and do not help us at all. If we find a positive argument, it will help us to advance in our suspicion of that particular disease, while, if we find a negative argument, it will make the disease less likely. The more powerful is an argument to confirm or exclude a hypothesis, the more it will increase or decrease the disease probability, respectively.

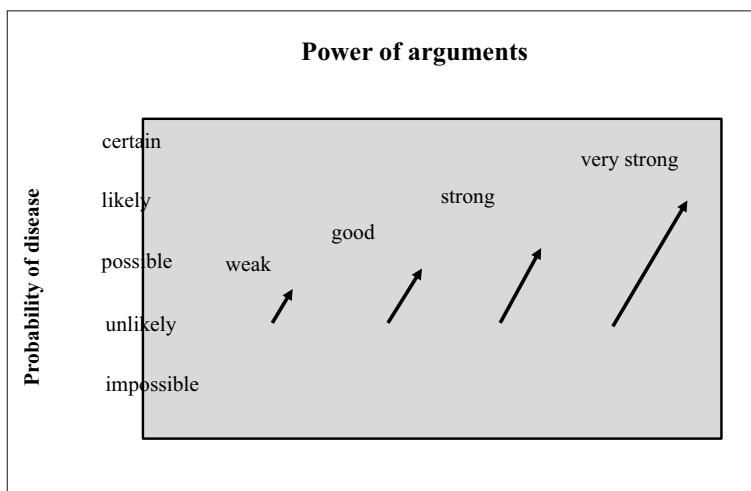
The "art" of the expert clinician is to immediately look for "strong" arguments, either to confirm or to reject a hypothesis.

Is there an objective way to define the power of an argument? This is precisely what we will try to discover in this chapter.

The basic properties of an argument

As is intuitive, a strong argument (if it is present, or positive) will make us advance more in the suspicion (or

probability) of a given disease than a weak one (figure). The opposite will happen of course with negative arguments. But how can we say if an argument is "weak", "good", "very good", "strong" or "very strong"? It is clear that, if we are able to define precise criteria to assess the power of clinical arguments and tests, our clinical reasoning will become much more effective!



The confirming power (CP) of an argument

In the paediatric ward of a rural hospital in Uganda, an 8-year-old girl presents with high fever and headache;

she had convulsions twice in the last 24 hours; the physical exam reveals a stiff neck.

We suspect meningitis. We have four arguments, and intuitively they don't have the same power to confirm our suspicion of bacterial meningitis: any one would say that a stiff neck is the most powerful argument, followed by the convulsions, the headache and the fever.

When we ask a student why a stiff neck is a powerful argument for meningitis, an immediate reply is often: "because most children with meningitis present with a stiff neck"; objection: the fever is almost always present in meningitis, too, then the two arguments are equally powerful! But a clever student will object: "yes, but there are many other children with fever!"

This is precisely the point: in order to assess if an argument is strong (for a particular disease), we do not only need to know how frequently it is present in that disease, but also how frequently it is present in the other patients (who may have any other disease). Let us call "true positive" (TP), for a given argument in a given

	Disease present	Disease absent
Test +	TP	FP
Test -	FN	TN

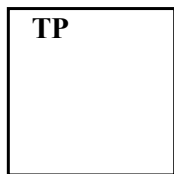
Is this a good test??

disease, the proportion of people affected by the disease who present the argument (the white square); then we will call "false positive" (FP) the proportion of other patients not affected by this disease who also present the same argument (the black square); we do not care of the negative results, FN and TN (the grey squares) so far, as we are discussing the confirming power, that is, the power of a present, or positive, argument.

It is intuitive that if an argument is equally present in people affected by the disease and in all others (as in the graph), it is of no value at all to confirm the hypothesis, or in other words: its confirming power is null or worthless.

Let's go back to our clinical example, the suspicion of meningitis in a girl.

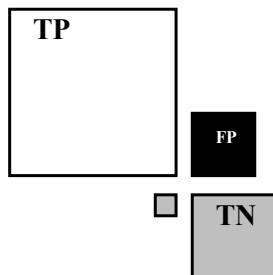
We will compare the first two arguments we have considered, the fever and a stiff neck.



The proportion of true positive (over the total of cases of meningitis) will be basically the same for the two arguments: as we said, if we only considered this proportion, we could not say which argument is stronger to confirm the clinical suspicion (as some will remember, the proportion of true positive is referred to as SENSITIVITY in classical epidemiology).

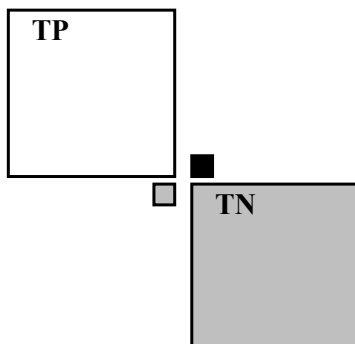
What is different for the two arguments is the proportion of false positive (the proportion of OTHER patients presenting the same argument).

Let's consider the fever first:



A relatively high proportion of patients with other diseases present fever, too (especially if we are in a malarious region!), therefore the ratio between TP and FP is not very high. The confirming power of the fever is not very good. In other words, we can say, as is visually intuitive, that fever doesn't help very much to discriminate between meningitis and other diseases.

Now let's see what happens with the neck stiffness:



Very few people with other diseases present a neck stiffness, and the ratio TP/FP is clearly very high: this argument is very helpful in discriminating between meningitis and other diseases: its confirming power is very high.

We can easily have a numerical value representing the confirming power. The proportion of true positive (the sensitivity) is roughly the same for both arguments, let's say 98%. The proportion of false positive is, say, 30% for fever (patients with other diseases, but not meningitis, who present with fever), and only 2% for neck stiffness (this is a rare argument in other disease, although a small number of feverish children without meningitis may present a stiff neck, too).

Let's represent these figures in a classical table, considering the fever first:

Fever	MENINGITIS	<i>OTHER</i>	Ratio (CP)
Present (+)	98	30	3.2
Absent (-)	2	70	
	100	100	

The confirming power of the fever for the suspicion of meningitis is **3.2**

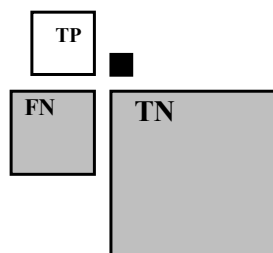
Neck stiffness	MENINGITIS	<i>OTHER</i>	Ratio (CP)
Present (+)	98	2	49
Absent (-)	2	98	
	100	100	

The confirming power of the fever for the suspicion of meningitis is 3.2, while that of the neck stiffness is **49**. These numbers do not tell us too much up to now, nevertheless it is clear that the numerical value of the CP is much higher for the neck stiffness than for the fever. We will learn how to deal with these numerical figures later on.

Consider that an argument may also be rarely found in a particular disease, and yet have a strong confirming power!

A young man in northern Angola presents with fever: surprisingly, at the thick film, instead of malaria parasites, we found some slender forms of trypanosome!

The thick film is not very sensitive in *T. gambiense* infection: only a minority of affected people presents a positive film. Nevertheless, the finding of trypanosomes in the peripheral blood of any other patient is extremely rare (you would say impossible, but never forget that a laboratory error can always occur!).

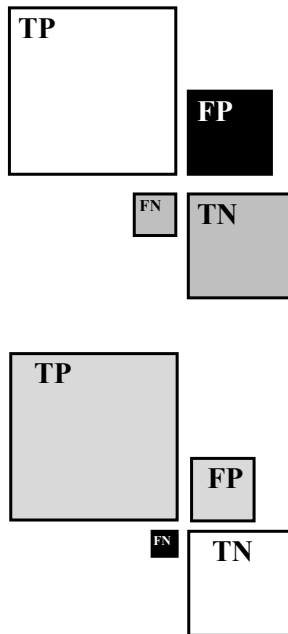


Then, for trypanosomiasis and thick film:

We notice that, although the proportion of true positives among the patients is low (less than 50%), the proportion of false positive is far lower! Therefore the ratio between TP and FP is still very good, and we can conclude that this argument has a very strong confirming power. It is true that the ratio between the true negative and the false negative is not good at all, but it is not of interest in this case, as the test's result was positive (that's why we left the negative results in grey).

In a Region of a Central American country some years ago, the Regional Epidemiologist was urgently called to investigate a recent outbreak of typhoid fever in a district. Almost 100 cases had been reported in the last two weeks, while only 7 cases had been diagnosed in that zone during the previous 6 months! The epidemiologist rushes to the affected zone just to discover that the origin of the "outbreak" coincides with the distribution to the health centres of the Widal test, which was not previously available! The survey reveals that most "cases" had no fever at all!

What was the mistake in this case? We often have a kind of excessive respect for laboratory tests, which, we think, are "hard data", compared with the "soft" clinical arguments. In reality this is often not the case! The Widal test is not really a very strong argument: many people without a typhoid will show a positive serology (or in other words, the percentage of false positive is quite high, as in the following graph): nevertheless, because of the "new" test result, even people without fever were diagnosed as typhoid cases!



In this series of examples, we have been dealing with positive results; therefore we have only been interested in the upper zone of each graph, while we have left the negative results (either true or false negative) in grey. The last example (the “false” typhoid outbreak) is a good one to introduce us to the complementary notion of the excluding power.

The excluding power of an argument

To begin with, it is clear that if we have to assess the excluding power (the power of an argument to reject the hypothesis we are thinking at) we are now interested in negative, rather than positive results. An argument can have a confirming power when it is present, or positive, and an excluding power when it is absent, or negative. This is just intuitive.

Let's consider the last example, the case of typhoid. Many cases were diagnosed despite the absence of fever. Let's examine this situation (fever as an argument of typhoid).

The confirming power of the fever would not be very good, for the same reasons that we have discussed for meningitis (although most patients present with fever, this symptom is very common in many other situations, too). But now we are not interested in the confirming power (we left the upper zone in grey), as fever is absent: what we are interested in is now the **excluding power** of the fever: how strong is this argument to exclude the hypothesis of typhoid, when it is absent?

Intuitively, the excluding power is represented by the ratio between the true negative (the white square) and the false negative (the black square): as virtually all patients with typhoid have fever, this ratio is very high, and so is the excluding power of the fever for the diagnosis of typhoid. If we compare this with the previous graph, it is clear that the excluding power of the fever is much stronger than the confirming power of the Widal test, and we can easily conclude that it is a nonsense to diagnose a typhoid in a patient with a positive Widal but without fever!

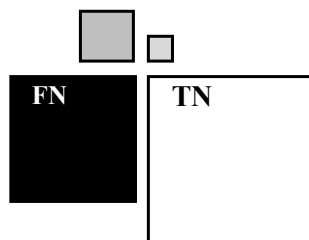
The concept of excluding power is a milestone not only of clinical epidemiology (or in “clinical logic”), but also of the good scientific method as a whole! In face of any new scientific hypothesis, the good scientist will thoroughly look for any possible arguments or data to refute his own hypothesis; not yet satisfied, he will present the hypothesis to the scientific community explicitly with the purpose of disproving it; and only when the new hypothesis will have resisted to all challenges and attempts to reveal that it is false, then the scientist will accept it (temporarily, and “until the contrary is proven”).

The same is true in the medical work. One of the commonest logical errors is what we call the “flirt error”, that is, we immediately “fall in love” with the first diagnostic hypothesis and from now on we will only look for arguments in favour, just disregarding those which do not fit with our hypothesis. This is strictly linked to the “tunnel error”, that is, we are so keen in demonstrating that our hypothesis is true, that we simply forget to consider any other possible explanation of that given clinical presentation.

Of course, we should not overestimate the excluding power of an argument and reject too early a hypothesis, either!

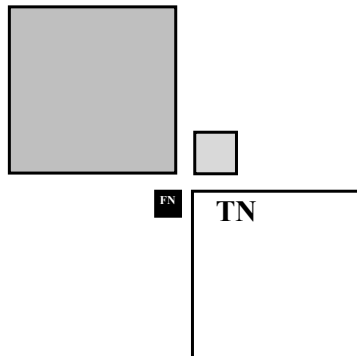
A young prostitute in Bangkok consults for a lower abdominal pain. We suspect an extra-uterine pregnancy, but the abdomen shows no resistance at palpation, and therefore we rule out the hypothesis.

Is that correct? Let's examine the properties of this argument.



Many patients with an E.U.P. will have no abdominal resistance (the black square), and therefore the ratio TN (white square) and FN is very low: the **EXCLUDING POWER** of this argument for a E.U.P. is almost null, and I cannot yet reject the suspicion. I will have to look for a stronger argument.

The patient says she had her last period 20 days earlier, this makes a pregnancy unlikely, but I want to exclude it with a Gravindex, which gives a negative result.



Let us analyse the properties of this new argument:

Only a small proportion of patients with an EUP will have a negative Gravindex, while most other patients will be negative (of course, the situation would radically change if we were in an antenatal clinic!!). Therefore we can say that this test has a strong excluding power for an EUP and we can now concentrate on other possible explanations of her symptoms.

Only the two lower squares determine the excluding power (as it refers to negative, not positive results!): the comparison between the two last examples shows that the proportion of false negative especially influences it.

Likelihood ratios

Let's go back to the classical epidemiological language to see the correspondence of the concepts of confirming and excluding power with the classical definitions that we normally meet in textbooks and publications.

We have been dealing with the four possible issues of any medical test or argument: the TP (TRUE POSITIVE: proportion of patients affected by the disease who have a positive test); the FP (FALSE POSITIVE: proportion of patients NOT affected by the disease but who have a positive test); the FN (FALSE NEGATIVE: proportion of patients affected by the disease who have a negative test); and the TN (TRUE NEGATIVE: proportion of patients not affected by the disease who have a negative test). In the classical epidemiological language, the TP represent the SENSITIVITY of a test or an argument, while the TN represent the test SPECIFICITY.

Unfortunately, neither of these classical concepts is sufficient to define the POWER of a test either to confirm or refute a hypothesis. We have discovered that the CONFIRMING POWER is best expressed by the ratio TP/FP, while the EXCLUDING POWER is the ratio TN/FN.

In the classical language, the "confirming power" is referred to as POSITIVE LIKELIHOOD RATIO (LHR+), representing, in fact, the ratio between the likelihood of finding this argument in people with the disease and the likelihood to find it in people without the disease. As for any ratio, it is more influenced by the denominator, therefore, as is quite intuitive, the LHR+ is more influenced by the SPECIFICITY (or, to be precise: by the FP rate, that is, $1 - \text{specificity}$), than by the SENSITIVITY (the TP rate) of an argument.

Let's verify this intuitive notion with some examples.

$$\text{CP or lhr} + = \text{sensitivity} / (1 - \text{specificity})$$

$$\text{or: } TP/FP$$

Let's see how the CP or lhr + is influenced by the sensitivity and specificity, respectively.

a. Argument 1: sensitivity: 90%

specificity: 90%

$$\text{CP or lhr} + = 90/10 = 9$$

Let's see what happens by increasing the sens. to 99%, leaving unchanged the specificity:

b. Argument 2: sensitivity: 99%

specificity: 90%

$$\text{CP or lhr} + = 99/10 = 9.9$$

There is an only marginal gain: but let's see what happens if we leave unchanged the sensitivity at the initial value of 90% and increase the specificity to 99

c. Argument 3: sensitivity: 90%

specificity: 99%

$$\text{CP or lhr} + = 90/1 = 90$$

This time the gain in lhr+ is a factor 10, (9 to 90).

Now we will decrease the sensitivity to 50% (the specificity remaining at the initial value of 90%)

d. Argument 4: sensitivity: 50%

specificity: 90%

$$\text{CP or lhr} + = 50/10 = 5$$

There is only a marginal decrease in lhr from 9 to 5. Finally, let's decrease the specificity by leaving the sensitivity at the initial value:

e. Argument 5: sensitivity: 90%

specificity: 50%

$$\text{CP or lhr} + = 90/50 = 1.4$$

In conclusion, it is possible to confirm mathematically the intuitive rule that the confirming power (or $lhr+$) is more influenced by the FP rate: the lower is the FP rate (or: the higher is the specificity), the higher is the confirming power.

If the specificity were 100%, we would not have any FP, and with 0 as denominator the confirming power of that argument would be infinite (in medical terms, we would say that this argument is **patognomonic**). A patognomonic argument is **the proof of the presence of a disease** when it is present, regardless the other arguments. Patognomonic arguments are quite rare in medicine, but when they are present, we shouldn't miss them! (Try to list 10 patognomonic arguments, both in internal and in tropical medicine).

In the classical language, the NEGATIVE LIKELIHOOD RATIO (LHR-), represents the ratio between the likelihood of finding a NEGATIVE RESULT in people with the disease and the likelihood to find it in people without the disease [5].

$$LHR- = (1 - \text{sensitivity})/\text{specificity} \text{ or: } FN/TN$$

The LHR- will tend to 0 if the sensitivity is very high: in fact, the stronger the LHR- (or the power of an argument to refute a hypothesis), the lower its numerical value. Therefore it is difficult to work with the LHR-, which tend to 0 if it is very strong, and to compare it with the LHR+ which tends to the infinite.

We prefer to work with the **excluding power**, which is just the reverse of the LHR- (that is TN/FN):

$$EP = \text{specificity}/(1 - \text{sensitivity})$$

$$\text{or: } TN/FN^1$$

In other words, the excluding power represents the ratio between the likelihood of finding a NEGATIVE RESULT in people without the disease and the likelihood to find it in people with the disease, and it is immediately comparable with the confirming power.

As we can see with the same examples as before, the EP is more influenced by the changes in sensitivity than in specificity.

a. Argument 1: sensitivity : 90%	
specificity: 90%	EP = 90/10 = 9
b. Argument 2: sensitivity: 99%	
specificity: 90%	EP = 90/1 = 90
c. Argument 3: sensitivity : 90%	
specificity : 99%	EP = 99/10 = 9.9
d. Argument 4: sensitivity : 50%	
specificity : 90%	EP = 90/50 = 1.4
e. Argument 5: sensitivity: 90%	
specificity: 50%	EP = 50/10 = 5

If the sensitivity were 100% (or: if there were no false negative) the **EP** would be **infinite**, the equivalent of **patognomonic** for a negative result: a corresponding term doesn't exist, although we could call such an argument **mandatory** (obligatorily required: its absence is the proof of the absence of the disease). Mandatory arguments are more frequent in medicine than patognomonic ones (try to find examples from your experience and medical knowledge!); in some sense, we could say that it may be easier to refute a hypothesis than to confirm it: a reason more to challenge our hypothesis with as many negative arguments as we can find!

Remember: **both the confirming and the excluding power of an argument increase by increasing the sensitivity and the specificity, but the former is much more affected by specificity, the latter by sensitivity.**

¹In the classical textbooks and publications you will normally find the LHR- with the classical formulas

Symmetry between the confirming power and the excluding power

*The Spanish Bishop of a Latin American city is admitted for a high fever of two week duration in a referral European hospital while he is on holidays, with no other major complain. He has a high WBC count and a high ESR. The blood film is negative and so is also the result of serial blood cultures and viral and bacterial serologies. The young intern suspects a liver abscess but the senior consultant says that two **typical** arguments are missing: he has no pain nor tenderness at the right upper quadrant, and the stool exam is negative for amoeba trophozoites. As he does not improve despite a broad range antibiotic treatment, three days later a CT scan is performed revealing an abscess in the right lobe: the serology turns out to be positive for *E. histolytica* at a high titre.*

What was the mistake in this case? The consultant thought that the absence of two **typical** arguments (that is: arguments with a high CONFIRMING POWER) made the diagnosis unlikely. But in fact, both arguments are frequently missing in a liver abscess: while their presence may have a good confirming power, their absence has a weak excluding power, as their sensitivity is low.

Many arguments in medicine are **asymmetrical**: either they have a good confirming power or a good excluding power, but rarely both. In other words **strong confirmers** are frequently **bad excluders**, and **strong excluders** are frequently **bad confirmers**.

In particular a **patognomonic** argument is almost never **mandatory** (see above), and vice versa.

Conclusion

Any argument for a given disease has a given confirming power and a given excluding power.

These powers are based on two theoretical properties, the sensitivity and the specificity, which are of little utility in clinical medicine; the classical epidemiological terms are the positive and negative likelihood ratio, respectively.

1. **Any clinical argument has a confirming power and an excluding power**
2. **They are rarely symmetrical**
3. **The powers may be mathematically represented by the likelihood ratios**
4. **The sensitivity and the specificity are data derived from research, which need be re-calculated as confirming and excluding power to be useful in clinical work**

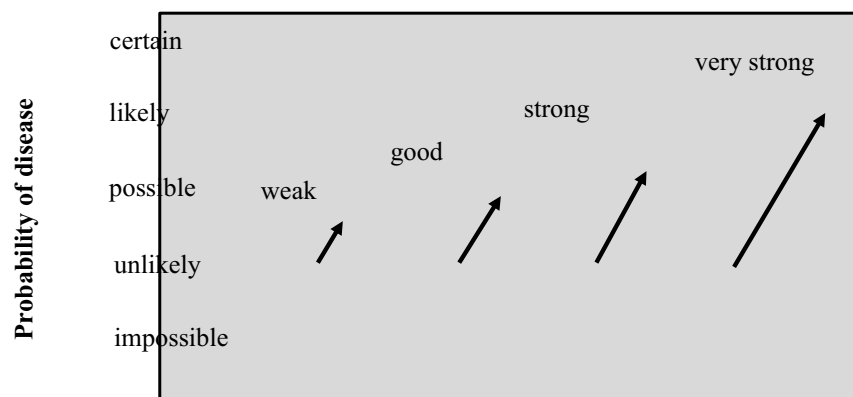
III – THE DIAGNOSTIC ROUTE: HOW TO COMBINE THE ARGUMENTS

Introduction

In the previous chapter we have learnt the confirming power (CP) and the excluding power (EP) of an argument for a given disease, and we now also know how to calculate their numerical value, as TP/FP and TN/FN, respectively. We don't know yet the real meaning of this numerical value: while we understand that a CP of 50 is stronger than a CP of 12, we are not yet able to apply this notion to see the evolution in the probability of a given disease when these arguments are used, or in other word we don't know yet how to move in the "diagnostic route".

Clearly, the progress of the disease probability is related to the power of the arguments, as is shown below.

Power of arguments



The starting point

Where does the *diagnostic route* start?

In the maternity ward of an Italian Hospital a primiparous woman is admitted, already in labour and is submitted to a routine ELISA test for HIV. Unfortunately the result is positive and the gynaecologist slips it out during his visit at the ward on Sunday. Both the woman (who does not belong to any risk group) and her husband are obviously upset! The gynaecologist knows that the test is a very good one, with around 99% sensitivity and 99% specificity, therefore he is convinced that the test is truly positive, nevertheless he tells the poor woman that there is still a possibility of a wrong result and only a more precise exam (Western Blot, to be carried out in the following days) can confirm the infection with certainty. Predictably, this does not reassure at all the poor woman, her happiness for the imminent delivery being switched to despair.

The husband, just as desperate, comes to see you, the clinical epidemiologist, in order to have a better explanation!

Was the gynaecologist right? How would you assess the real probability of this woman really being infected with HIV? How would you explain the situation to the couple?

Let's examine the test properties first

ELISA	HIV	OTHER	
+	99	1	CP=99
-	1	99	EP=99
	100	100	

It is in fact a very good, **symmetrical** test with both a strong excluding and confirming power, 99, that we may round off to 100. Over 100 HIV infected individuals, only 1 would be erroneously found negative (FN), and over 100 non-infected, only 1 would be erroneously found negative (FP). Therefore, of the 100 possible positive results, 99 are true positive, which seems to confirm the gynaecologist's point of view.

But this would be only true if the chances of the woman to be HIV infected, before the test, were 50% (100 infected, 100 non-infected).

In reality, with no test, we would say that the woman has no more than 1/10.000 possibility of being HIV positive (prevalence in Northern Italy outside the risk groups). Let's take this information into account before doing the test, which of course maintains its sensitivity and specificity (inner square), but is now applied to the real risk of 1/10.000

To understand this, imagine to test a hypothetical population of 10.000 women like this, 1 of them being infected by HIV: (1 infected, 9.999 non infected), and see what happens: the one infected will almost certainly been classified as positive (0.99 that I may round off to 1), but among the other 9.999 I will have 1% of false positive, that is 99.99 (rounded as 100).

As the test result is positive, I am only concerned with the upper part of the table:

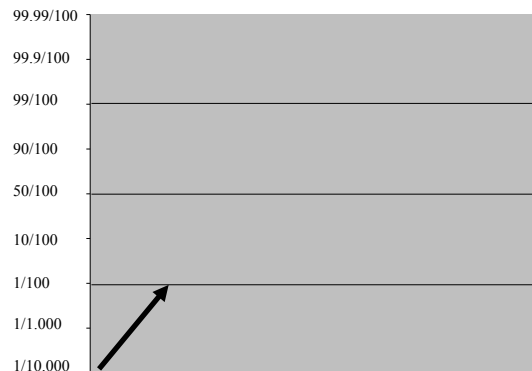
	INFECTED	NOT INFECTED
test HIV +	1	100
test HIV -	0	9900
total	1	9.999

Over 101 positive results, only 1 is a true positive (TP), while 100 are FP. Therefore a positive result has only 1/101 probability of being a TP, that is to say that the woman, after the test, had only 1% probability of being truly infected! This is a spectacular example of how our initial intuition may be wrong, when we forget that a test is not an absolute value, but that we always apply a test to a patient, each patient being different, each one with a different suspicion, or risk of disease.

A Western Blot was urgently carried out on Monday to definitely reassure the woman, and expectedly gave a negative result.

The positive ELISA (strong test CP 100) had increased the probability of infection by two steps in this particular probability scales, from 1/10.000 to 1/100 (graph below).

Gain in probability after the ELISA test



In an Infectious Disease department about 50% of the patients admitted in one year are HIV infected. The doctor is going to see a new patient, he already knows that he has a positive ELISA. Before seeing the patient: how many probabilities does he have of being really infected with HIV?

	INFECTED	NOT INFECTED				
test HIV +	99	1				
	<table><tr><td>99</td><td>1</td></tr><tr><td>1</td><td>99</td></tr></table>	99	1	1	99	
99	1					
1	99					
test HIV -	1	99				
total	100	100				

The test is exactly the same, but the hypothetical population is now completely different: over 200 randomly selected patients, 100 are infected and 100 are not.

Of 100 positive results 99 are TP, therefore the chance of a new patient of being infected are 99%. The test was exactly the same, the only difference being the “suspicion pre-test” or “pre-test probability”

On our probability scales, the steps are two again, from 50 to 99%.

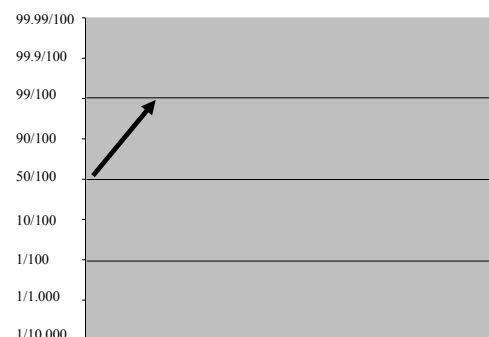
A real clinical example

A young patient is admitted with fever, history of weight loss, chronic diarrhoea, a generalised adenopathy, a oesophageal candidiasis; he admits having made use of injectable drugs up to two years ago and also admits a very promiscuous sexual behaviour. The WBC count is normal but the total lymphocytes are only 600. In face of a high suspicion of AIDS (he has never been tested before) an ELISA HIV is carried out, giving a negative result.

The patient is submitted to broad-spectrum antibiotic treatment, the fever improves a little, and eventually he is discharged with no diagnosis.

Did the doctors make a mistake? Once again, we have to assess the prior probability of this patient being

Gain in probability after the ELISA test



infected with HIV. In facts, he meets the case definition of AIDS, before doing the test, and we would say that his real probability is at least 99.9%. Once again, let's apply the test to a hypothetical population of 1000 patients like this: the test has now given a negative result (therefore we are interested in the lower part of the table): over 11 possible negative results, 10 are FN and only 1 is TN, therefore the doctor should have

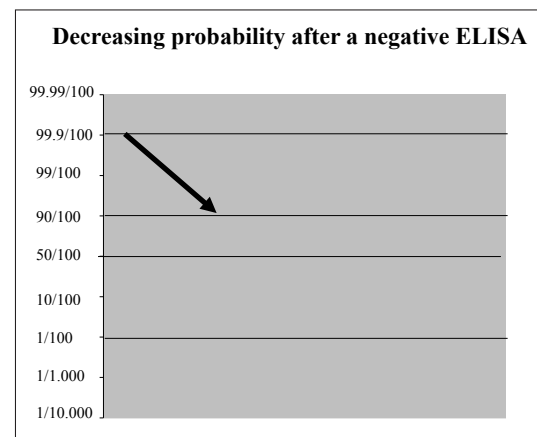
	INFECTED	NOT INFECTED				
test HIV +	989	0				
	<table><tr><td>99</td><td>1</td></tr><tr><td>1</td><td>99</td></tr></table>	99	1	1	99	
99	1					
1	99					
test HIV -	10	1				
total	999	1				

considered that the patient had still 90% probabilities of being affected by AIDS!

This was case happened in the Internal Medicine department of an European Hospital. The same day, an old nun in the surgery department turned out to be HIV positive!

Never forget that, besides the test sensitivity and specificity, one should always consider the possibility of a mistake, such as an exchange of samples at one of the various step of the transfer of blood samples to the laboratory!

Now: let's examine once again what happens on the probability scales: this time we have a negative test, its EP is 100, and once again the movement (downward this time) on the scale is 2 steps, from 99.9 to 90%.

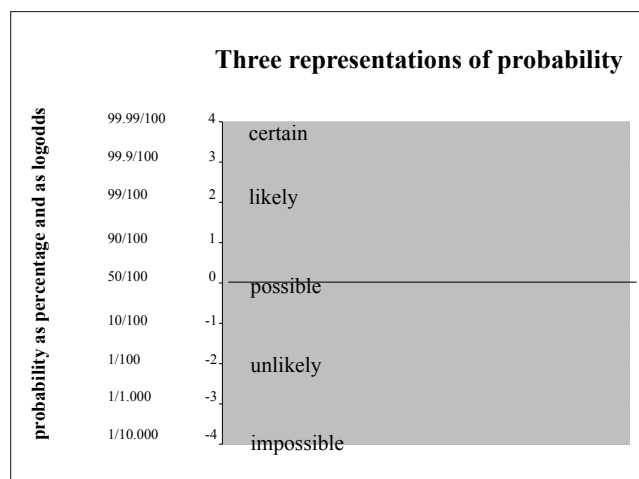


Moving on the diagnostic scale on the basis of the power of the arguments

More in general, it is possible to show that, on such a scale (for the more familiar: it is a **logarithmic**, not a linear **scale**), [6, 7] any test with a EP of 100 moves the probability two steps up or downward, respectively; a power of 10 corresponds to 1 step; a power of 1,000 corresponds to 3 steps (such very strong arguments are very rare indeed). In fact, in such a scale, the probabilities are first transformed into they respective "odds", or "chances", which are then expressed as their logarithms (**logodds**) in a very simple numerical scale going, for instance, from -4 (corresponding to 1/10.000) to +4 (corresponding to 9,999/10.000 or 99.99%).²

The graph besides shows the correspondence between the probabilities and the respective logodds: the advantage is that one can work just with the simplified log scale henceforward, and directly apply the powers of the arguments on this scale.

In order to work with such a scale, the numerical values of the CP and EP have also to be converted



²The mathematical demonstration of these concepts is beyond the scope of this chapter. A mathematical appendix is under elaboration

into their respective logarithms. The log value of 10 is 1, the log of 100 is 2, the log of 1000 is 3 and so forth. The log value directly corresponds to the steps on the scale (up or downward according to the confirming or excluding power).

What matters for the clinician is not to do complex calculation on a table, but rather to have a rough estimate of the powers of the clinical arguments and tests for a given disease, which could be simply expressed as “+” or “-“ for the confirming and the excluding power, respectively.

The table below gives a useful classification of the arguments, based on their powers, so that they can be directly used on the probability scale.

Tabella 1 - A discrete numerical/qualitative classification of the confirming (CP) and excluding (EP) powers

Numerical value of CP or EP	CP (symbolic representation)	EP (symbolic representation)	Steps on the log scale (=log value of powers)	Definition
	?	?	0	null
3 (2 to 5)	~	~	0.5	weak
10 (6 to 16)	+	-	1	good
30 (17 to 57)	+~	~	1.5	strong
100 (58 to 200)	++	--	2	very strong

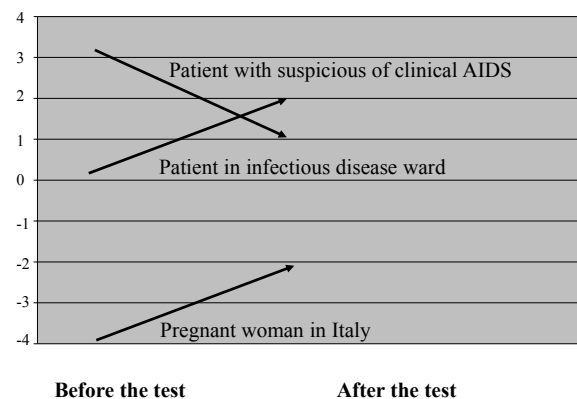
Arguments stronger than 200 do exist, but they are rare in medicine.

Let's compare the three cases of HIV ELISA on the simplified log scale:

A strong (and symmetric) test, with both a logCP and a logEP of 2, moves the probability by two steps (upward or downward, respectively) on the log scale, regardless the starting point.

In general, the steps on the scale correspond exactly to the log power of the arguments.

Change in probability before and after the ELISA test



How to do it with more arguments (serial arguments)

As we said in the chapter on the decision threshold, the ultimate purpose of the clinical work with an individual patient is to take the right decision. The threshold is the basic element of the fundamental decision in most cases, that is: to treat or not to treat for that particular disease. Now that we have learnt how to use the arguments and their respective values on a simplified (log) scale, we should be able to determine if we have reached the threshold or not, at the end of our diagnostic work with that particular patient.

A 35-year-old patient in Ghana presents for an episode of frank hematemesis. He had the same symptom 15 days ago. He has no fever nor any other major complain, in particular he has never suffered from epigastric pain. At the examination he is not ascitic, but he presents a gross splenomegaly. You suspect a late S. mansoni bilharziasis (the patient lives in an endemic area). He refers a history of recurrent diarrhoea with blood, but he has never had it during the last few months. You ask a stool exam, which is negative for schistosoma eggs. The laboratory shows a slight eosinophilia (8%). What to do? Is it justified to treat him for schistosomiasis?

First, we should establish the threshold: the disease is very serious, the treatment may be still effective even at this late stage and practically harmless: you would surely accept to treat 9 patients without schistosoma rather than leave 1 affected patient untreated. If so, your threshold would be around 10% (or -1 on the log scale). Now, the arguments.

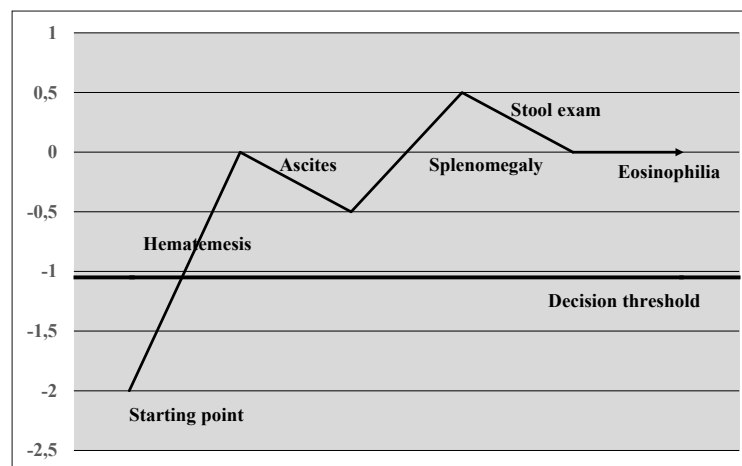
Tabella 2 - Power of the arguments used in the case (for the suspicion of late *S. mansoni*)

Argument	Confirming Power	Excluding Power
Hematemesis (present)	++	
Ascites (absent)		~
Gross splenomegaly (present)	+	
Stool exam (negative)		~
Slight eosinophilia (present)	? (null)	

Now let's examine the evolution of the disease probability. What is the starting point in an endemic zone? We can admit that about 1/100 of the admitted patients are affected by the disease.

Let's plot the "diagnostic route" on the simplified scale.

We have two positive arguments with a strong and a good CP, respectively (hematemesis and splenomegaly); two negative (absent) arguments with a weak EP (ascites and the stool exam) and a positive argument with a null power (a slight eosinophilia is a very common finding in endemic areas for parasites!). Therefore, after the five combined arguments, the disease probability is now of 0 on the log scale, which corresponds to 50%, well over the decision threshold!



CONCLUSION

In the previous chapter we had learnt how to evaluate the power of an argument and to express it as the numerical value of the TP/FP ratio (confirming power) and of the TN/FN ratio (excluding power), respectively. Now we have learnt how to apply each argument to the previous suspicion of disease (the "starting point" on the scale); we have also learnt how to combine the arguments powers on a simplified (log) scale which comes quite close to our intuition, in order to decide if we have reached the decision threshold. Of course, a constant exercise is required in order to easily apply the method, but the complex mathematics and the use of tables for calculations are no longer necessary!

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PUBBLICATO CON IL CONTRIBUTO DI



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