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Laurea Magistrale in Medicina e Chirurgia

**Cost-effectiveness of the italian screening protocol
for international adoptees**

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*“Every single minute matters,
every single child matters,
every single childhood matters.”*

- Kailash Satyarthi, Indian children's rights activist

Abstract (Italian)

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Abstract

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Abbreviations

HIV	H uman I mmunodeficiency V irus
STI	S exually T ransmitted I nfection
FASD	F eto A lcohol S pectrum D isorders
MCV	M ean C orpuscular V alue
VBA	V isual B asic for A pplications

Chapter 1

Introduction

Children's health has historically always been a sensitive and concerning matter for humankind. We can find the reason for this in our universal instinctive draw towards the protection and care for our offspring, and in how children can be struck by some of the most devastating and life-wrecking diseases. Sometimes, these are the phenotypical expression of genetical marks, scarred onto and into these kids. Despite the origin, the color of the skin or the culture the child bears in his or her lineage, human beings feel the need to raise and safeguard them from all harms, on a physical, emotional and spiritual level. This is one of the strongest biological calls to action in all human experience.

Thus, pediatrics must care and remember that children's health and well-being must be guarded across political borders, across poverty, across starvation. This thesis, and the paper it's so deeply bound to set themselves to renew this vow.

1.1 Intercountry and international adoptees

International adoptees are children with special needs: a vulnerable pediatric population with a chronic condition that requires access to a wide variety of health care services (as defined by [7] and [8]); they are recognized as a group of children

requiring medical attention (see [11]). Compared to 19% of the general population, approximately 39% of adopted children require special healthcare attention (as extensively explained in [1]). They are of school age, part of a sibling group, members of historically oppressed racial or ethnic groups, or they have considerable physical, emotional, or developmental need: all potential elements of vulnerability endangering the child's healthy upbringing. This is not a limited problem: annually more than 30.000 kids are adopted across countries, and, in the United States, of all 136.000 national adoptees in 2008, almost 25% come from foreign countries; U.S. families adopted 22.884 children in 2004, mostly from China (which accounts for 33% alone), Ethiopia, Russia and South Korea (see [1]), 8.868 more in 2012 and 4.714 in 2017 (see [3]). It's estimated that more than 125.000 children have been adopted in the United States alone since 1986 (source can be found in [11]). Further data on annual U.S. international adoptions and their social and financial costs can be found at [4]. More in-depth medical issues will be discussed in Section 1.2.

Although personal experiences obviously vary, most children placed for international adoption have some history of poverty and social hardship in their home countries, and approximately 65% are adopted from orphanage or institutional settings (as stated in [11]). As explained in [1], the effects of institutionalization and other early life stress impact all areas of early growth and development. As a result, many children require specialized support and understanding to overcome such impacts and to reach their full potential.

Moreover, as in [2], internationally adopted children may withstand a number of juridical and social impairments even after adoption. No generalization can be made on this matter though since laws and policies greatly differing among countries. They may be stripped of their name (a.e. in Cape Verde, Argentina and Turkey), have no right to inheritance (a.e. in Republic of Moldova and France), see the termination of the relationship with birth parents and relatives (a.e. in Japan, Albania and Togolese Republic), lose their citizenship and not acquire a new one (a.e. Hungary and New Zealand), or even bear limitations on marriage in their adult life (a.e. in Argentina and France). These boundaries are to be considered associated to the emotional and psychological stress of new surroundings, new affections, new habits, and even

new climatic environments (which can be clinically relevant, as explained in 1.3.2.2). All these elements account for some of the factors that contribute to the hardships an adoptee must endure throughout his life and call for a strong action from pediatric physicians and social services employees, as possible support figures which may change these kids' lives forever.

1.1.1 Levels and trends in intercountry adoption worldwide

International adoption is increasingly considered a measure of last resort worldwide, if the child's birth family or community are unable or unwilling to care for him anymore (see [1]), justifying the downward trend on international adoptions across the globe.

The United Nations Population Division estimates that about 40.000 intercountry adoptions took place each year around 2005, accounting for 15% of the total number of adoptions (see [2]). As shown in Table 1.1 and 1.2, the involved countries, both for destination and origin, are relatively few.

Destination countries are led by the United States with over 127.000 total adoptions in 2001. Even though it accounts for nearly half of all adoptions, only 15% of American families decide to take care of a child coming from outside the US. France and Spain (both with significant annual adoptions, ranging from 4,000 to 5,000 adoptions per year), instead, embrace 80-90% of all adoptions from foreign lands, although they have far less total adoptions per year. Almost all countries adopt primarily from China and Russia, confirming data are shown in 1.2. The median percentage of international adoptions in all examined countries is 64 a remarkable value and effort in helping children from developing countries.

The Italian adoption status will be discussed in 1.1.2.

Rank	Receiving country ¹	Number	Percentage	Main country of origin
1	United States of America	19.056	15	China
2	France	3.995	90	Haiti
3	Spain	3.951	82	Russia
4	Italy	2.177	68	Russia
5	Germany	1.919	34	Russia
6	Canada	1.875	46	China
7	Sweden	1.093	65	China
8	Netherlands	1.069	78	China
9	Denmark	688	55	China
10	Norway	664	76	China
11	Switzerland	558	79	Colombia
Median		370	64	

TABLE 1.1: Countries of destination with the largest number of intercountry adoption.

Source: United Nations Population Division report (see [2])

Countries of origin are better balanced throughout the globe, with China leading the chart, followed by Russia, Guatemala, and Ukraine. Guatemala and Ethiopia stand out for the exceptional percentage of international adoptions among all, with 97% and 93% respectively. As clearly shown in Table 1.2, the United States is the preferred destination country for most of the listed nations.

All of the countries listed below struggle with some sort of social hardship: political instability, poverty, inequality, starvation, ethnic or civil wars, complex and violent pasts. Eyes can't be closed and mouths shut, when it so obviously portrayed that children are the ones paying from these adulthood failures. They must run, be saved, separated, deported in order to be granted one single chance, one single hope.

Rank	Receiving country ¹	Number	Percentage	Main receiving country
1	China	8.644	19	United States
2	Russia	5.777	25	United States
3	Guatemala	3.726	97	United States
4	Ukraine	2.672	35	United States
5	Korea	2.258	58	United States
6	Vietnam	1.419	49	United States
7	India	1.098	36	United States
8	Bulgaria	1.010	44	Italy
9	Kazakhstan	948	26	United States
10	Colombia	846	60	France
11	Ethiopia	810	93	France
Median		50	34	

TABLE 1.2: Countries of origin with the largest number of intercountry adoption.

Source: United Nations Population Division report (see [2])

In Table 1.3 the leading countries both of origin and of destination have been divided for the most oriented towards international adoptions out of all national adoptions per year. Belgium, France, and Luxembourg lead the receiving side; Ethiopia, Guatemala, Mali, and Thailand the origin side, instead, with over 90%.

¹Only countries with more than 500 adoptees per year were included. For the complete table, please see the referenced source.

60 to 74%	75 to 89%	90% or more	60 to 74%	75 to 89%	90% or more
Andorra	Cyprus	Belgium	Colombia	Georgia	Ethiopia
Australia	Liechtenstein	France	Latvia	Haiti	Guatemala
Israel	Netherlands	Luxembourg	Grenada		Mali
Italy	Norway		Honduras		Thailand
Singapore	Spain		Niger		
Sweden	Switzerland		Togo		
(A) Receiving Countries			(B) Countries of origin		

TABLE 1.3: Countries with the highest percentual international adoptions.
Source: United Nations Population Division report (see [2])

As explained in [5] and [6], in recent years, international adoption rates have been dropping. As shown in the Figure 1.1, the United States’ foreign adoptions have dramatically fallen from 18.856 children per year in 2000 to 2.681 in 2016: more than 75% has been cut. This isn’t a U.S. isolated problem, though; world-wide international adoption rates are on the fall in the past two decades, due to policy changes in the countries of origin. In recent decades South Korea, Romania, Guatemala, China, Kazakhstan and Russia, all former leaders in foreign adoption (see [2] and Table 1.2), have banned or cut back on international custody transfers. For example, the number of Guatemalan children adopted by foreign parents dropped from 4100 in 2008 to a stunning 58 in 2010 (in Figure 1.1), after the country drastically curtailed the practice and China decreased its foreign adoptions by 86% in a decade (in Figure 1.1).

As policies change, it’s often stated that it’s in “the best interest of the child”, a point usually supported by a strong media-driven high-profile infantile abuse or neglect case. These incidents are rare: only a 0.03% rate. In Russia, on the other hand, the rate of child abuse is about 25 times higher. Such statistics call into question whether the child’s best interest is really why countries have been canceling international adoption. Authors have found that political pressures and international

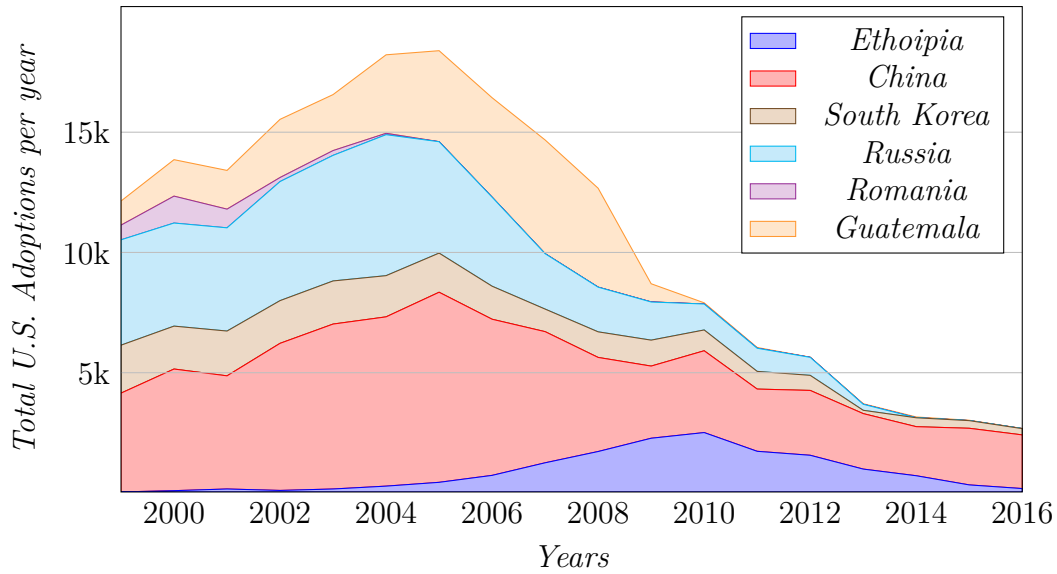


FIGURE 1.1: Adoptions to US by top countries from 1999 to 2016.

Source: U.S. State Department

embarrassment can spur countries to halt adoptions. After the *moratorium* on foreign adoptions in Guatemala, a former member of the country’s National Adoption Council expressed pride. “Our image as being the number one exporter of children has changed”, he said. “Guatemala has dignity”, again, he added.

Moreover, poor countries often struggle to meet The Hague Convention policy’s high standards, which include creating a central adoption authority, accrediting local agencies and tightening approval procedures, making such a rigorous international regulation more expensive. Fees have been applied to agencies, adoptive parents, orphanages, and countries. This 1993 global agreement, signed by 103 countries in 2016, which meant to make adoption safer and more straightforward, has contributed to their decline.

Foreign adoptions can’t solve global poverty. But ending them merely punishes thousands of vulnerable kids and their potential parents worldwide. And that’s in nobody’s best interest.

1.1.2 International adoption in Italy

According to [7], [8] and [9], in 2014 Italy was the European country with the highest rate of adoptions and the second one worldwide, following the United States. This major role was confirmed in the next two-year period: 2.716 children were adopted from foreign countries in 2016/17 (see [10]), keeping Italy second worldwide for international custody transfers (see [5] and [6]). As of [2], in 1999 Italy was the fourth country worldwide for international adoptions with 2.177 international adoptions, amounting to 68% of national total. Most of the Italian adoptees are from the Russia Federation (as shown in Table 1.1) and Italy is Bulgaria's favorite country of destination (in Table 1.2).

Region	Year 2016		Year 2017	
	Value	Percentage	Value	Percentage
Lombardia	258	16,7	179	15,3
Veneto	151	9,8	125	10,7
Lazio	145	9,4	112	9,6
Toscana	144	9,3	124	10,6
Campania	132	8,5	99	8,5
Puglia	123	7,9	85	7,3
Emilia-Romagna	119	7,7	86	7,4
Piemonte	93	6,0	69	5,9
Sicilia	68	4,4	44	3,8
Calabria	55	3,6	37	3,2
Liguria	52	3,4	39	3,3
Friuli-Venezia Giulia	43	2,8	34	2,9
Marche	42	2,7	39	3,3
Umbria	29	1,9	20	1,7
Trentino-Alto Adige	26	1,7	18	1,5
Sardegna	26	1,7	17	1,5
Abruzzo	20	1,3	28	2,4
Basilicata	13	0,8	85	7,3
Molise	9	0,6	1	0,1
Valle d'Aosta	0	0,0	0	0,0
Total	1.548	100	1.168	100

TABLE 1.4: Intercountry adoptions by Italian regions, years 2016 and 2017.

Source: Italian Presidency of Council of Ministers, Commission for International Adoptions. See [10].

Table 1.4 shows that Lombardia, Veneto, and Lazio were the leading Italian regions for international adoption in 2016-2017, followed by Toscana and Campania. *De facto*, the northern and central portions of the country are the most active adoption-wise. Overall and regional numbers are dropping, in the same manner as it is happening all over the globe, as explained in Section 1.1.1, but a few exceptions

stand out. Abruzzo and Basilicata increased their annual adoptions, from 20 to 28 (the first), and from 13 to 85 (the latter). Even more exceptional is Valle d'Aosta, that scored a flat *zero* in both years. It must be said, though, that it's the least populated region, with only 125.000 people living in the whole region.

Most of these children, between 40 and 50%, span between 5 and 9 years of age at their arrival in Italy, and less than 15% are really young (younger than one-year-olds) or the older ones (older than 10).

In 2016 and 2017, the most fertile countries of origin are the same in both years, even though they swap internal ratings: Russian Federation, Colombia, India, Hungary, Poland, Vietnam, Brazil, and China (as stated in [10]). The children from these countries amount to 73% of the total international adoptions.

1.2 Role of the pediatrician

Internationally adopted children come from countries with many endemic diseases, including hepatitis B, tuberculosis and many different intestinal parasites (as explained in [11]). These children have lived in crowded conditions, sometimes with poor standards of hygiene and inadequate nutrition. These children are malnourished, often suffer from emotional and physical neglect, environmental deprivation, and are therefore vulnerable to infectious diseases. And although children must obtain medical clearance as part of the process of applying for a visa to travel around the globe, the evaluation is usually cursory, therefore unreliable. The physician appointed to establish this sketchy health status certificate is directed to evaluate the child for "serious contagious diseases or disabilities". However, no blood testing is required or other screening is mandated unless risk factors are identified.

According to [14], more than 50% of internationally adopted children, regardless of sex, age, and country of origin, will have a previously undiagnosed medical condition, which is identified on initial evaluation. Therefore, adoption-medicine specialized pediatricians should advise prospective parents on appropriate testing of the child after arrival in the country of destination. Early screening is crucial in order to

identify eventual pathological conditions and to prevent what could be irreversible damage. Many studies (a.e. see [7] and [28]) have assessed prevalence of all infections, ranging between 35 and 42% for all infections, 40% for parasitic ones (see [23] and [26]), and between 5 and 19% for tuberculosis (see [26] and [27]).

As can be found in [12], [13], [23], and the more recent [16], the American Academy of Pediatrics recommends careful health screening of all newly arrived international adoptees.

Reference [1] states that results of specific diagnostic studies and laboratory tests performed in the country of origin should not be relied on and should be repeated once the child arrives in the country of destination. Paradoxically, review of the child's medical records may raise more questions than provide answers, because of poor translation and use of medical terminology and medications that are unfamiliar to trained physicians. Each medical diagnosis should be considered carefully before being rejected or accepted.

Therefore what screening tests should be ordered by physicians caring for newly arrived international adoptees? In addition to hepatitis A, B and C, HIV, congenital syphilis, other STIs, intestinal parasites, and tuberculosis by Mantoux testing, experts also recommend testing for anemia, thyroid and renal disease, vision and hearing defects, and newborn metabolic disorders when appropriate, along with careful monitoring of growth and development (according to [11], [14], [7], and [8]). In this matter, particular attention should be paid to FASD, as [7] and [8] suggest; according to these studies, more than 17% of all internationally adopted children evidenced special needs, in which FASD is the most common condition observed. Chansoff *et al.* in [25], in a sample of 547 foster and adopted children reported that 86.5% children with FASD had never been previously diagnosed. Special attention should be paid to children originating from Russia.

Moreover, [11], [14], [12], [15], [16], and [17] are only some of the examples of a medical literature full to the brim, which compels physician to test for adequate immunization status for vaccine-preventable disease. Pre-adoptive immunization records may not be assumed as truthful or correct, according to [15]. As discussed in [16], this may happen because the *cold chain* gets interrupted, vaccines are used

beyond expiration dates, they are poorly stored or they are given incorrectly, too early or too far apart. Therefore, guidelines suggest that all internationally adopted children, with or without any official immunization records, should always be tested for their immunization status as soon as they come to the adopting country, in order to perform vaccinations whether serum antibody titers are inadequate. At this regard, Italian laws (see [18] and [19]) suggest re-vaccinating subjects who have unknown, incomplete or undocumented vaccination status, without even checking for residual immunization.

As [24] points out, families of internationally adopted children face risks associated with travel if they pick up their children overseas. Unlike other travelers, though, they also face risks because of close contact with a child with uncertain infection and vaccination status. Some of these transmissible infections may be inapparent or may be not manifest in adopted children until many years after the adoption, posing risks to the well-being of these children's new families and communities.

Although concern about HIV infection causes considerable anxiety, very few internationally adopted children have arrived with this infection (see [11]). Either HIV-infected children do not survive long enough to complete an international adoption procedure or local screening identifies infected children and removes them from consideration for adoption.

Internationally adopted children have often experience pre- and perinatal complications, such as exposure to drugs and alcohol during gestation, the absence of perinatal care, low birth weight, and prematurity (see [24]). Although this is widely known and well documented, several systematic reviews and eminent periodicals focused on infectious disease risk among internationally adopted children, while data regarding prevalence and spectrum of non-infectious conditions, including special needs, FASD and labio-palatal schisis, are poor (see [7] and [8]).

One medical peculiarity is that even the most recent literature reviews concerning international adoptees' health evaluation, vitamin D serum levels are usually left out. This is contradictory with many other papers (see [29], [30], [31], and [32]) that strongly advise towards the relevance of this test for the well being of the child. Internationally adopted children often suffer from vitamin D deficiency or

insufficiency, because of the profound change in latitude they experience during the adoption phase, or because of malnutrition combined with lack of solar exposure during pre-adoptive care, usually in orphanages.

There is no reasonable doubt that vitamin D deficit is one of the most relevant medical issues among internationally adopted children and it is mandatory for the pediatrician to test and appropriately treat this disorder.

Table 1.5 summarizes the recommendations of the American Academy of Pediatrics (source: *Nelson - Textbook of Pediatrics*, 20th Edition. See [1]), as follows:

Screening tests	
Complete blood cell count	
Hemoglobin identification	
Blood lead level	
Urinalysis	
Newborn screening ²	
Vision and hearing screening	
Developmental testing	
<i>Other screening tests to consider based on clinical findings and age of the child</i>	
Detection of <i>Helicobacter pylori</i> antibody or ¹³ C-urea breath test	
Stool cultures for bacterial pathogens	
<i>Glucose-6-phosphate dehydrogenase</i> deficiency screening	
Sickle cell	
Urine pregnancy test	
Screening tests for infectious diseases	
<i>Recommended tests</i>	<i>Optional tests</i>
Hepatitis B virus serologic testing: <i>HBsAg</i> and <i>anti-HBs Ab</i> ³	<i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> testing
Hepatitis C virus serologic testing ³	Chagas disease serology
Hepatitis A virus serologic testing	Malaria thick and thin smears
Varicella virus serologic testing	Urine for O&P for schistosomiasis ⁴
Syphilis serologic testing: Treponemal and Non-treponemal tests	
Human immunodeficiency viruses 1 and 2 testing ^{3,5}	
Complete blood cell count with red blood cell indices and differential	

Stool examination for ova and parasites (2
or 3 specimens)
Stool examination for *Giardia lamblia* and
Cryptosporidium antigen (1 specimen)
Tuberculin skin test or interferon- γ release
assay^{3,6}

TABLE 1.5: American Academy of Pediatrics' recommended screening tests for international adoptees upon U.S. Arrival

On the other hand, pediatricians must be warned about the psychosocial risks derived from considering an adoptee as such a *fragile creature*. As illustrated in [12], prior to adoption, or at the time of entry into the family unit, the pediatrician should begin a careful medical assessment of the child and should counsel the family appropriately regarding adoption issues. Pediatricians should be alert to the following potential problems:

1. Some parents expect the guarantee of a “perfect child”. They may push for unnecessary tests and expect unrealistic predictions from the pediatrician. Just as a birth family cannot be certain that its natural child will be healthy, the adoptive family cannot be guaranteed that a child will not have future health problems.
2. By focusing on an extensive medical evaluation of a child, the pediatrician must be careful not to create a “vulnerable” child through an exaggerated assessment of historical risk. Most adopted children are healthy, or at least can become so, even if they come from high-risk backgrounds. Certainly, the risks must be defined and then carefully explained to the family, so that problems can be anticipated and dealt with expediently. This is the same anticipatory guidance the pediatrician uses for all patients.

²Only for children younger than 12 months of age.

³To be repeated 3-6 months after arrival.

⁴Only if hematuria is present.

⁵ELISA if the child is older than 18 months; PCR if he or she is younger than 18 months.

⁶Followed by a chest X-ray if the test results in hive or induration are bigger than 5 mm

3. It is not the pediatrician's role to judge the advisability of a proposed adoption, but it is appropriate and necessary that the prospective parents and any involved agency be apprised clearly and honestly of any special health needs detected now or anticipated in the future.

Thus, the pediatrician should resist unreasonable demands while still being empathic with the adoptive parents' anxieties and concerns.

Lastly, the sanitary surveillance on internationally adopted children, both clinical and test-based, in Italy is based in 20 centers, one per region. In Friuli-Venezia Giulia, this center is placed in *San Vito al Tagliamento*, where the data for this paper has been collected. For a more in-depth overview of the work they do on a day-to-day basis, see the Introduction to Chapter 2 on page 18.

1.3 Illnesses and dysfunctions under exam

Lorem ipsum dolor sit amet, consectetur adipiscing elit. Pellentesque nibh metus, suscipit a scelerisque sit amet, rhoncus et lectus. Mauris eget erat rutrum, euismod massa id, maximus mauris. Nulla maximus, ex sit amet lacinia consequat, enim ante mollis dui, sit amet tincidunt massa felis id magna. Aenean gravida ante nec volutpat rutrum. Cras eget ullamcorper leo. Curabitur eu volutpat tellus. Integer nec ornare sapien. Fusce ipsum justo, interdum quis libero a, mattis tristique velit. Phasellus rhoncus lorem non ultrices luctus.

1.3.1 Infectious diseases

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nec ornare sapien. Fusce ipsum justo, interdum quis libero a, mattis tristique velit. Phasellus rhoncus lorem non ultrices luctus.

1.3.1.1 Tuberculosis

it can occur.

1.3.2 Blood count disorders and deficiency states

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1.3.2.1 Iron-deficient anemia

it can occur.

1.3.2.2 Vitamin D deficiency

it can occur too.

1.3.3 Height-weight disorders

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ante mollis dui, sit amet tincidunt massa felis id magna. Aenean gravida ante nec volutpat rutrum. Cras eget ullamcorper leo. Curabitur eu volutpat tellus. Integer nec ornare sapien. Fusce ipsum justo, interdum quis libero a, mattis tristique velit. Phasellus rhoncus lorem non ultrices luctus.




Chapter 2

Materials and Methods

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2.1 The population in exam

Our study sample is highly representative of the original population, since $x\%$ (20/32) of the IAC adopted in Friuli-Venezia Giulia in the study period were included. The study period spanned from 2002 to 2017. They increased year after year. This is shown in graph 2.1, where:

1. Africa is displayed .
2. Eastern Europe is displayed .
3. Latin America is displayed .

4. Asia is displayed █.

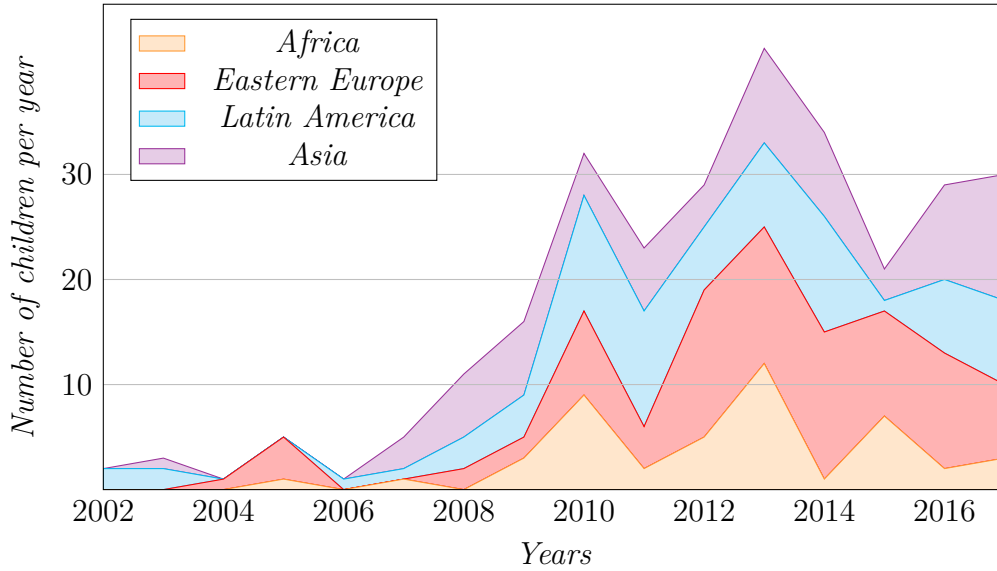


FIGURE 2.1: Our population distribution - Total of children visited via the screening protocol, stratified by geographic area of origin

2.1.1 Inclusion and exclusion criteria

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2.2 The data set

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massa id, maximus mauris. Nulla maximus, ex sit amet lacinia consequat, enim ante mollis dui, sit amet tincidunt massa felis id magna. Aenean gravida ante nec volutpat rutrum. Cras eget ullamcorper leo. Curabitur eu volutpat tellus. Integer nec ornare sapien. Fusce ipsum justo, interdum quis libero a, mattis tristique velit. Phasellus rhoncus lorem non ultrices luctus.

2.3 Data set elaboration

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2.3.1 VBA expressions

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All VBA expression can be found in Appendix A at page 28.

2.3.2 Cut-off values

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2.3.2.1 Haemoglobin

This was a little prick, but we managed with [36] (from WHO). It depends on:

1. Sex
2. Age
3. Altitude (looking only at sea level)

Based on Haemoglobin levels, we stratified anemias in:

1. Non-Anemia
2. Mild
3. Moderate
4. Severe

This is summarized in Table that follows.

2.3.2.2 MCV

This was ANOTHER little prick, but we managed with [37].

2.3.2.3 Circulating Iron

This was easy.

2.3.2.4 MCV

This was ANOTHER little prick, but we managed with [37].

2.3.2.5 Vitamin D

Vitamin D is healthy. We dosed 25OH or *colecalfiferol* (1,25(OH)₂D: 1,25-dihydroxyvitamin D and 25(OH)D: 25-hydroxyvitamin D)...

Recent literature has openly discussed about how vitamin D deficiency should be defined, especially in pediatric age. [33] is a really strong and recent (2018) Italian review on vitamin D deficiency. Another review is in [34]. From BMJ is [35]. And maybe strongest of all the letter addressed to BMJ from the British Society of Pediatric Radiology and child protection and nutrition committees of the Royal College of Pediatrics and Child Health in [38].

General international consensus is on defining cut-off values based on alkaline phosphatase and calcium levels so to enhance ONLY bone health, ignoring the now well-known vitamin D extra-skeletal effects.

2.3.3 Parasites grouping

2.4 Statistical Analyses

Le analisi descrittive sono state condotte utilizzando frequenze e percentuali per variabili categoriche, e medie e deviazioni standard o mediane e intervalli interquartili per variabili continue, con una preferenza per queste ultime a causa del campione esiguo di dati che non consente di verificare la normalità dei dati.

La differenza nei valori di variabili continue in diversi gruppi è stata valutata con test non parametrici di Mann-Whitney o Kruskal-Wallis a seconda che i gruppi da confrontare fossero due o più di due. Per lo studio di associazione tra due variabili dicotomiche, o tra una variabile dicotomica e una categoriale ordinata abbiamo utilizzato il test esatto di Fisher a due code. Per studiare se un esito dicotomico fosse associato a una o più variabili indipendenti abbiamo utilizzato la regressione logistica. Per studiare la relazione tra due variabili continue, abbiamo preferito utilizzare la correlazione per ranghi di Spearman.

Per tutte le analisi abbiamo usato il software Stata/IC 14.2 (StataCorp LLC, College Station, USA).

Chapter 3

Results

3.1 Introduction

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3.2 Risultati 1

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nec ornare sapien. Fusce ipsum justo, interdum quis libero a, mattis tristique velit. Phasellus rhoncus lorem non ultrices luctus.

3.3 Risultati 2

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3.4 Risultati 3

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Chapter 4

Discussion

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4.1 Objectives achieved

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4.2 Our recommendations

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4.3 Future work

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Appendix A

Data set elaboration: VBA expressions

This appendix provides all the code used in this thesis to elaborate the data set. Visual Basic for Application (VBA) is the programming language chosen for this purpose, as the most effective and manageable way of elaborating data in excel sheets. Further information can be found throughout this thesis, especially in Section 2.3 at page 20 and cut-off values, parameter by parameter, can be found at Section 2.3.2

In the following appendix, cells are indicated as combination of a letter (identifying the column) and a number (identifying the line), as they originally were in the database. Every line represents a single child's evaluation; every column represents one of the examined parameters. The full column-parameter correspondence can be found in following Table A.1.

Column	Parameter	Units or cell type	Description
<i>A</i>	First and last name	<i>text</i>	The name of the kid. ¹
<i>B</i>	Sex	<i>text</i>	The sex of the child, as <i>M</i> or <i>F</i> .

¹Although registering the patient's full name exposed the research to a possible privacy breach risk, it was added nonetheless to easily identify each patient as the data set got larger through the years.

<i>C</i>	Age (in months)	<i>months</i>	The age of the child. Further information on how this was obtained can be found at Section A.1.
<i>D</i>	Age (in years)	<i>years</i>	The age of the child.
<i>E</i>	Country of origin	<i>text</i>	Where the child comes from.
<i>F</i>	Geographic area of origin	<i>text</i>	<i>E – field</i> was divided in 4 macro-geographic areas. See Section A.2 for further information.
<i>G</i>	Time in Italy	<i>months</i>	Months spent in Italy before being examined by our physicians.
<i>H</i>	Weight	<i>percentile</i>	Percentile in which the child fits for his weight at time of examination.
<i>I</i>	Pathological weight	<i>boolean</i>	Is the child underweight for his or her age?
<i>J</i>	Height	<i>percentile</i>	Percentile in which the child fits for his height at time of examination.
<i>K</i>	Pathological height	<i>boolean</i>	Is the child short for his or her age?
<i>L</i>	Haemoglobin	g/dl	Used to determine whether the child is anemic.
<i>M</i>	Pathological haemoglobin	<i>boolean</i>	Is the child anemic?
<i>N</i>	MCV	fl	Mean corpuscular volume of red blood cells. This was used to evaluate anemias and determine whether they were secondary to iron (<i>microcytic</i>) or Vitamin B ₁₂ (<i>macrocytic</i>) deficiencies.
<i>O</i>	Pathological MCV	<i>boolean</i>	Is the <i>N – field</i> low, high or normal?
<i>P</i>	Circulating iron	µg/dl	How much free iron is circulating in the child's blood?
<i>Q</i>	Pathological circulating iron	<i>boolean</i>	Is the <i>Q – field</i> low or not?
<i>R</i>	Ferritin	ng/ml	Amount of circulating ferritin. This was used to confirm iron-deficiency anemia.
<i>S</i>	Pathological ferritin	<i>boolean</i>	Is the <i>R – field</i> low or not?

<i>T</i>	Feces	<i>text</i>	List of microorganisms found in triple direct microscopical exams on three fecal samples. The “ <i>negative</i> ” string was used to indicate negativity to all examinations.
<i>U</i>	Group 1 parasites	<i>boolean</i>	Is the <i>T – field</i> positive for one of the following parasites?
<i>V</i>	Entamoeba	<i>boolean</i>	Is the child infected with <i>Entamoeba</i> ? This parasite belongs to Group 1.
<i>W</i>	Ancylostoma	<i>boolean</i>	Is the child infected with <i>Ancylostoma</i> ? This parasite belongs to Group 1.
<i>X</i>	Trichuris	<i>boolean</i>	Is the child infected with <i>Trichuris</i> ? This parasite belongs to Group 1.
<i>Y</i>	Group 2 parasites	<i>boolean</i>	Is the <i>T – field</i> positive for one of the following parasites?
<i>Z</i>	Giardia	<i>boolean</i>	Is the child infected with <i>Giardia</i> ? This parasite belongs to Group 2.
<i>AA</i>	Strongyloides	<i>boolean</i>	Is the child infected with <i>Strongyloides</i> ? This parasite belongs to Group 2.
<i>AB</i>	Hymenolepis	<i>boolean</i>	Is the child infected with <i>Hymenolepis</i> ? This parasite belongs to Group 2.
<i>AC</i>	Blastocystis	<i>boolean</i>	Is the child infected with <i>Blastocystis</i> ? This parasite belongs to Group 2.
<i>AD</i>	Endolimax	<i>boolean</i>	Is the child infected with <i>Endolimax</i> ? This parasite belongs to Group 2.
<i>AE</i>	Immunization status	<i>text</i>	<i>Complete, incomplete</i> or <i>negative</i> immunization statuses on mandatory vaccines in Italy.
<i>AF</i>	HCVab	<i>boolean</i>	Is the child positive to hepatitis C antibodies?
<i>AG</i>	HBsAg	<i>boolean</i>	Is the child positive to the hepatitis B superficial antigen?

<i>AH</i>	HBVab	<i>boolean</i>	Is the child positive to hepatitis B antibodies?
<i>AI</i>	HIV	<i>boolean</i>	Is the child positive to HIV antibodies?
<i>AJ</i>	Lue	<i>boolean</i>	Is the child positive to syphilis antibodies?
<i>AK</i>	Vitamin D	ng/ml	<i>25-hydroxycholecalciferol</i> serum levels.
<i>AL</i>	Pathological Vitamin D	<i>boolean</i>	Is <i>AK</i> – <i>field</i> deficient?
<i>AM</i>	Mantoux	<i>boolean</i>	Did the Mantoux turn out positive?
<i>AN</i>	Mantoux hive size	mm	Dimensions of the Mantoux hive size.

TABLE A.1: Full column-parameter correspondence, including units of measurement or cell type and a short description

A.1 Age (in months)

This VBA expression checks the *Age (in months)* (column C) and, if it's not empty, it divides it's value by 12, rounding it down, just as age counting works.

The `ROUNDOWN` function was implemented in order to avoid overestimating child's age.

```
=IF(
  C2 <> " ";
  ROUNDDOWN(
    C2 / 12;
    0
  );
  " ")
```

A.2 Geographic area of origin

To further understand how geographic origin influenced the results of our screening program, the countries of origin were grouped up in 4 major continents or areas with the following excel expression. The chosen macro-areas were:

- Africa
- Asia
- Eastern Europe
- Latin America

```
=IF(  
  OR(  
    E2 = "Russia";  
    E2 = "Albania";  
    E2 = "Bulgaria";  
    E2 = "Hungary";  
    E2 = "Ukraine";  
    E2 = "Moldavia";  
    E2 = "Romania"  
  );  
  "Eastern Europe";  
  IF(  
    OR(  
      E2 = "Burkina Faso";  
      E2 = "Ethiopia";  
      E2 = "Ivory Coast";  
      E2 = "Congo";  
      E2 = "Guinea Bissau";  
      E2 = "Africa";  
      E2 = "Ghana";  
      E2 = "Benin"  
    );  
    "Africa";  
    IF(  
      OR(  
        E2 = "Colombia";  
        E2 = "Brazil";  
        E2 = "Guatemala";  
        E2 = "Peru";
```

```
        E2 = "Costa Rica"
    );
    "Latin America";
    IF(
        OR(
            E2 = "Armenia";
            E2 = "India";
            E2 = "China";
            E2 = "Vietnam";
            E2 = "Sri Lanka";
            E2 = "Siberia";
            E2 = "Nepal";
            E2 = "Philippines"
        );
        "Asia";
        ""
    )
)
)
```

A.3 Pathological values

The data set contained numerical values for many laboratory analyses. Cut-off values for these results were established via the most recent literature review, as explained in Section 2.3.2. In the following sections, the code used to establish which ones were pathological and which were not, is displayed and shortly explained.

A.3.1 Weight and height

These parameters, since they had already been converted to percentile values, were easily implemented with the following simple VBA expression:

```
=IF(  
    H2 <> " ";  
    IF(  
        H2 <= 10;  
        1;  
        0  
    );  
    ""  
)
```

A.3.2 Haemoglobin

Hemoglobin required a more complicated and sophisticated expression, in order to be stratified, because hemoglobin pathological cut-offs depend on various factors, as described in Section 2.3.2.1. Moreover mild, moderate and severe anemias had to be separated in order to properly evaluate the child's health status; each one had an arbitrary value of 1 (*mild*), 2 (*moderate*) or 3 (*severe*) associated to it.

```
=IF(  
    L2 <> " ";  
    IF(  
        AND(  
            C2 >= 6;  
            C2 < 60  
        );  
        IF(  
            L2 >= 11;  
            0;  
            IF(  
                AND(  
                    L2 < 11;  
                    L2 >= 10  
                );  
                1;  
                IF(  
                    AND(  
                        L2 < 10;  
                        L2 >= 7  
                    );  
                    2;  
                )  
            )  
        )  
    )  
)
```

```

        3
    )
)
);
IF(
    AND(
        C2 >= 60;
        C2 < 132
    );
    IF(
        L2 >= 11,5;
        0;
        IF(
            AND(
                L2 < 11,5;
                L2 >= 11
            );
            1;
            IF(
                AND(
                    L2 < 11;
                    L2 >= 8
                );
                2;
                3
            )
        )
    );
    IF(
        AND(
            C2 >= 132;
            C2 < 168
        );
        IF(
            L2 >= 12;
            0;
            IF(
                AND(
                    L2 < 12;
                    L2 >= 11
                );
                1;
                IF(
                    AND(
                        L2 < 11;
                        L2 >= 8
                    );
                    2;
                    3

```

[illegible]

A.3.3 MCV

As just described for haemoglobin, MCV required more complicated techniques in order to be stratified, because of its variability (through age, sex, ecc...), as described in Section 2.3.2.4. Moreover, boolean results couldn't be accepted for this parameter, so arbitrary values were used to appropriately identify microcytic (1) and macrocytic (2) anemias.

```
=IF (
    N2 <> " ";
    IF (
        B2 = "F" ;
        IF (
            AND (
                C2 >= 0 ;
                C2 < 60
            ) ;
            IF (
                N2 > 85 ;
                2 ;
                IF (
                    AND (
                        N2 <= 85 ;
                        N2 >= 69
                    ) ;
                    0 ;
                    1
                )
            ) ;
            IF (
                AND (
                    C2 >= 60 ;
                    C2 < 120
```

```
);  
IF(  
    N2 > 89;  
    2;  
    IF(  
        AND(  
            N2 <= 89;  
            N2 >= 75  
        );  
        0;  
        1  
    )  
);  
IF(  
    AND(  
        C2 >= 120;  
        C2 < 168  
    );  
    IF(  
        N2 > 92;  
        2;  
        IF(  
            AND(  
                N2 <= 92;  
                N2 >= 78  
            );  
            0;  
            1  
        )  
    )  
);  
B2 = "M";  
IF(  
    AND(  
        C2 >= 0;  
        C2 < 60  
    );  
    IF(  
        N2 > 85;  
        2;  
        IF(  
            AND(  
                N2 <= 85;  
                N2 >= 71  
            );  
            0;  
        )  
    )  
);
```

```
1
)
);
IF(
    AND(
        C2 >= 60;
        C2 < 120
    );
    IF(
        N2 > 88;
        2;
        IF(
            AND(
                N2 <= 88;
                N2 >= 76
            );
            0;
            1
        )
    );
    IF(
        AND(
            C2 >= 120;
            C2 < 168
        );
        IF(
            N2 > 90;
            2;
            IF(
                AND(
                    N2 <= 90;
                    N2 >= 76
                );
                0;
                1
            )
        )
    )
);
""
)
);
""
)
```


A.3.4 Circulating iron

The following VBA expression was used to establish whether circulating iron levels were insufficient.

```
=IF(  
  P2 <> "";  
  IF(  
    AND(  
      P2 >= 16;  
      P2 <= 129  
    );  
    0;  
    1  
  );  
  ""  
)
```

A.3.5 Ferritin

The following VBA expression was used to identify pathological ferritin values. These were, again, stratified for *mild* (1), *moderate* (2) and *severe* (3) deficiencies.

```
=IF(  
  R2 <> "";  
  IF(  
    R2 >= 20;  
    0;  
    IF(  
      AND(  
        R2 < 20;  
        R2 >= 15  
      );  
      1;  
      IF(  
        AND(  
          R2 < 15;  
          R2 >= 10  
        );  
        2;  
      )  
    )  
  )  
)
```

```
        IF (
            R2 < 10;
            3
        )
    )
)
);
""
)
```

A.3.6 Vitamin D

The following VBA expression was used to establish whether Vitamin D (serum 25-hydroxycholecalciferol) values were *insufficient* (1), *deficient* (2) or *severely deficient* (3). The predictive choice for this marker is explained at Section 2.3.2.5.

```
=IF(
    AA2 <> "";
    IF(
        AA2 >= 50;
        0;
        IF(
            AND(
                AA2 < 50;
                AA2 >= 25
            );
            1;
            IF(
                AND(
                    AA2 < 25;
                    AA2 >= 10
                );
                2;
                IF(
                    AA2 < 10;
                    3
                )
            )
        )
    );
    ""
)
```

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