UNIVERSITÀ DEGLI STUDI DI TRIESTE
Dipartimento Universitario Clinico di Scienze Mediche, Chirurgiche e della Salute

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Health Status of Internationally Adopted Children: a Retrospective Study

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Laureando
Sebastiano Genna
Correlatore
Dott. Matteo Trevisan

Relatore
Prof. Egidio Barbi
Correlatore
Dott.ssa Laura Casali

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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)

In questo studio sono stati analizzati i dati demografici, clinici e laboratoristici di 285 bambini adottati tramite adozione internazionale provenienti da tutto il mondo e visitati presso il centro del GNLBI di San Vito al Tagliamento tra il gennaio 2002 e il dicembre 2017. Tutti i bambini sono stati sottoposti al protocollo diagnostico-assisteniale del GNLBI, il quale include una valutazione clinica completa, esami laboratoristici e strumentali, al fine di stimare la prevalenza di malattie infettive, stati carenziali e copertura vaccinale. Le condizioni morbose più frequentemente riscontrate sono state: anemia microcitica (8%), deficienza di vitamina D (40%), parassitosi gastroenterica (41%) e titoli anticorpali vaccinali insufficienti o assenti (65%). Tutte queste condizioni sono però trattabili e non severe. Il 17% dei bambini esaminati presentava inoltre una Mantoux positiva. Le infezioni più severe, come l'epatite B e C, l'infezione da HIV e la sifilide si sono riscontrate con estrema rarità, in accordo con la letteratura internazionale specializzata in medicina del bambino adottato e immigrato.

Inoltre, sono stati analizzati i costi e i benefici di buona parte del protocollo impiegato e si è concluso che l'emocromo, la Mantoux e la titolazione degli anticorpi vaccinali si configurano come esami a costi accettabilmente contenuti e grande impatto sul decorso clinico e terapeutico del bambino. Al contrario, i livelli sierici di vitamina D e gli esami atti a determinare la presenza di infezioni parassitarie gastrointestinali, da HBV, HCV, HIV e sifilide potrebbero non essere impiegati in uno screening di primo livello. Sono stati inoltri valutati l'impatto economico di queste analisi e i potenziali risparmi, se queste fossero accantonate.

In conclusione, la gran maggioranza dei bambini adottati tramite adozione internazionale gode di buona salute e solo pochissimi soffrono di patologie mediche maggiori. Nonostante il protocollo diagnostico-assistenziale del GNLBI sia una pietra miliare della pediatria del bambino migrante e adottato, crediamo ci sia spazio per migliorare, se letto in prospettiva di costi e benefici.

Abstract

We studied the demographic, clinical, and laboratory data from 285 internationally adopted children coming from all over the globe, brought to our attention at the GNLBI Center of *San Vito al Tagliamento*, between January 2002 and December 2017 to evaluate the prevalence of infectious diseases, deficiency states, and immunization status of international adoptees. All children underwent the *GNLBI diagnostic-aiding protocol*, including a physical, laboratory and instrumental examinations. Microcytic anemia (8%), vitamin D deficiency (40%), parasitic gastrointestinal infections (41%), and an incomplete or absent immunization coverage (65%) were the most frequent condition observed, all of which are treatable and non-life threatening conditions. 17% of all examined children presented a positive Mantoux test. More severe infections, such as hepatitis B and C, HIV infection, and syphilis were exceptional, in agreement with the most recent medical literature.

Moreover, we analyzed costs and benefits of sections of the protocol and concluded that blood count, Mantoux test and serum antibody titers of vaccine-preventable disease are highly valuable exams with a direct influence on the therapeutical path of the child. On the other hand, serum vitamin D levels and tests for parasitic gastrointestinal infections, HBV, HCV, HIV, and syphilis may not be so worthwhile. We also studied costs and potential savings.

In conclusion, most adoptive children had good general health, with only a few having major medical problems. Although the *GNLBI diagnostic-aiding protocol* is a milestone of adoption-specialized pediatrics, we believe there is room for improvement from a cost-benefit perspective.

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And lastly, to myself, for always believing that, even when your heart's lost all its hope, after dawn there will be sunshine.

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Abbreviations

GLNBI	**G**ruppo di **L**avoro **N**azionale per il **B**ambino **I**mmigrato
HIV	**H**uman **I**mmunodeficiency **V**irus
STI	**S**exually **T**ransmitted **I**nfection
ESR	**E**rythrocyte **S**edimentation **R**ate
FASD	**F**eto **A**lcohol **S**pectrum **D**isorders
MCV	**M**ean **C**orpuscolar **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 universal phenomenon is one of the most potent 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 profoundly 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 [1] and [2]); they are recognized as a group of children requiring medical attention (see [3]). Compared to 19% of the general population, approximately 39% of adopted children need special healthcare attention (as extensively explained in [4]). They are of school age, either part of a sibling group, members of historically oppressed racial or ethnic groups, or 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% came 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 [4]), 8.868 more in 2012 and 4.714 in 2017 (see [5]). It's estimated that more than 125.000 children have been adopted in the United States alone since 1986 (source can be found in [3]). Further data on annual U.S. international adoptions and their social and financial costs can be found at [6]. 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 orphanages or institutional settings (as stated in [3]). As explained in [4], 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 [7], 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 significantly differ 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 with the emotional and psychological stress of new surroundings, new affections, new habits, and even new climatic environments.
All these elements account for some of the factors that contribute to the hardships an adoptee must endure throughout his life and call for 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, applied only if the child's birth family or community are unable or unwilling to care for him anymore (see [4]), justifying the downward trend of 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 [7]). As shown in Table 1.1 and 1.2, the involved countries, both for destination and origin, are relatively few.

The United States led destination countries with over 127.000 total adoptions in 2001. Even though it accounts for nearly half of all approvals, 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 passages 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 Table 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 Section 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 [7])

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	Country of origin[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 [7])

In Table 1.3 the leading countries both of origin and destination have been listed. The most oriented towards international adoptions, out of all national adoptions per year, are: Belgium, France, and Luxembourg at the receiving side; Ethiopia, Guatemala, Mali, and Thailand at the origin side.

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[1] Only 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
Andorra	Cyprus	Belgium
Australia	Liechtenstein	France
Israel	Netherlands	Luxembourg
Italy	Norway	
Singapore	Spain	
Sweden	Switzerland	

(A) Receiving countries

60 to 74%	75 to 89%	90% or more
Colombia	Georgia	Ethiopia
Latvia	Haiti	Guatemala
Grenada		Mali
Honduras		Thailand
Niger		
Togo		

(B) Countries of origin

TABLE 1.3: Countries with the highest percentual international adoptions.

Source: United Nations Population Division report (see [7])

As explained in [8] and [9], over the last few years, international adoption rates have been dropping. As shown in Figure 1.1, the United States' foreign adoptions have dramatically fallen from 18.856 children per year in 2000 to only 2.681 in 2016: more than 75% has been cut. This isn't a US isolated problem, though; worldwide international adoption rates have been 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 [7] 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 4.100 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).

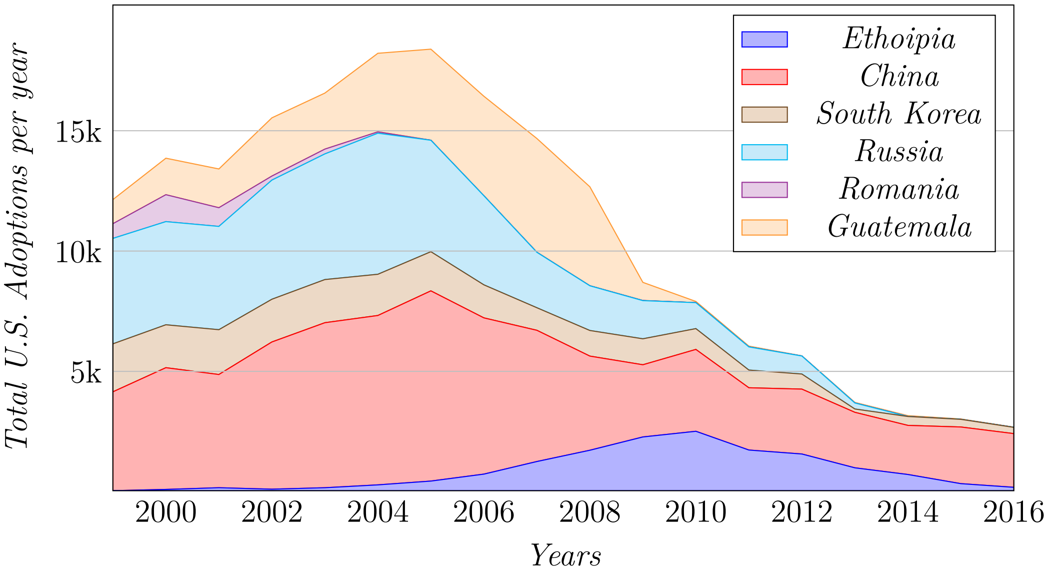

FIGURE 1.1: Adoptions to US by top countries from 1999 to 2016.

Source: U.S. State Department

As policies change, it's often stated that it's in *"the best interest of the child"*, a point usually supported by strong media-driven high-profile infantile abuse or neglect cases. These incidents are rare, though: only a 0.03% rate. The rates of child abuse in the countries of origin, on the other hand, are often higher. For example, Russia's rate is about 25 times higher. Such statistics call into question whether the child's best interest is really why countries have been cancelling international adoption. Authors have found that political pressures and international 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, developing 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 [1], [2] and [10], in 2015 Italy was the European country with the highest rate of adoptions and the second one worldwide, following the United States. This dominant role was confirmed in the next two-year period: 2.716 children were adopted from foreign countries in 2016-2017 (see [11]), keeping Italy second worldwide for international custody transfers (see [8] and [9]). As of [7], 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 Russian Federation (as shown in Table 1.1) and Italy is Bulgaria's favorite country of destination (in Table 1.2).

	Year 2016		Year 2017	
Region	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 [11].

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 mobile 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 of the country, 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 extremely young (younger than one year-olds) or older than 10 years old.

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 [11]). The children originating from these countries amount to almost 73% of the total international adoptions.

1.2 Role of the pediatrician

Internationally adopted children come from countries with many infectious endemic diseases, including hepatitis B, tuberculosis and many different intestinal parasites (as explained in [3]). These children have lived in crowded conditions, sometimes with poor standards of hygiene and inadequate nutrition. Most of the times they are malnourished, often suffer from emotional and physical neglect, environmental deprivation, and are, therefore, vulnerable to infectious diseases. 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, thus 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 [12], 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 potential pathological conditions and prevent what could be irreversible damage. Many studies (*a.e.* see [1] and [13]) have assessed prevalence of infectious diseases, ranging between 35 and 42% for all infections, almost 40% for parasitic infestations (see [14] and [15]), and between 5 and 19% for tuberculosis (see [15] and [16]).
As can be found in [17], [18], [14], and the more recent [19], the American Academy of Pediatrics recommends careful health screening of all newly arrived international adoptees.

Reference [4] states that the 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 state 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 physicians trained in the country of destination. 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 [3], [12], [1], and [2]). In this matter, particular attention should be paid to Feto Alcohol Spectrum Disorders (FASD), as [1] and [2] 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 [20], in a sample of 547 foster and adopted children reported that 86.5% children with FASD had never been previously diagnosed. Particular attention should be paid to children originating from Russia.
Moreover, [3], [12], [17], [21], [19], and [22] are only some of the examples of a medical literature full to the brim, which compels physicians to test for adequate immunization status for vaccine-preventable disease. Pre-adoptive immunization records may

not be assumed as truthful or correct, according to [21]. As discussed in [19], this may happen because the *cold chain* gets interrupted, vaccines are used beyond expiration dates, they are poorly stored, or they are incorrectly given, 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 [23] and [24]) suggest re-vaccinating subjects who have unknown, incomplete or undocumented vaccination status, without even checking for residual immunization.
As [25] 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 not be 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 amongst the general population, very few internationally adoptees were found positive to HIV testing (see [3]). 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 [25]). Although this is widely known and well documented, several systematic reviews and eminent periodicals focused on infectious disease risk among internationally adopted children. Data regarding prevalence and spectrum of non-infectious conditions, including special needs, FASD, and labio-palatal schisis, are poor (see [1] and [2]). At the time of adoption, many children exhibit delays in at least one area of development, but most show significant gains within the first 12 months after adoption. Those adopted before 6 months of age usually demonstrate healthy growth, whereas those adopted at older ages have more variable outcomes (see [4]). Careful monitoring of development within the first year of adoption can identify a "developmental trend" over time that may be more predictive of long-term functioning than assessment at any specific point in time.

One medical peculiarity is that even in the most recent literature reviews concerning international adoptees' health evaluation, vitamin D serum levels are usually left out. This omission is in contrast with many other papers (see [26], [27], [28], and [29]) 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 American Academy of Pediatrics (source: *Nelson - Textbook of Pediatrics*, 20th Edition. See [4]), as follows:

Screening tests
Complete blood cell count
Haemoglobin identification
Blood lead level
Urinalysis
Newborn screening[2]
Vision and hearing screening
Developmental testing
Other screening tests to consider based on clinical findings and age of the child
Detection of *Helicobacter pylori* antibody *or* ^{13}C-urea breath test
Stool cultures for bacterial pathogens
Glucose-6-phosphate dehydrogenase deficiency screening
Sickle cell
Urine pregnancy test

Screening tests for infectious diseases	
Recommended tests	*Optional tests*
Hepatitis B virus serologic testing: *HBsAg and anti-HBs Ab*[3]	Neisseria gonorrhoeae and Chlamydia trachomatis 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

Lastly, the sanitary surveillance on internationally adopted children, both clinical and test-based, is based in Italy 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 16.

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[2] Only for children younger than 12 months of age.

[3] To be repeated 3-6 months after arrival.

[4] Only if hematuria is present.

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

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

1.2.1 Watch out for the *fragile creature*

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 [17], 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. Indeed, 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.
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.

Chapter 2

Materials and Methods

As anticipated in Section 1.2 on page 10, internationally adopted children in Italy get tested in one of 20 centers, one per region. In Friuli-Venezia Giulia, this center is placed in *San Vito al Tagliamento*, where the data for this paper was collected. International adoptees are brought to this hospital by the adoptive parents as an autonomous decision or because adoption organizations or their trusted pediatrician have previously advised them to do so. The child is hospitalized for just one day. This is the minimum time required in order to obtain all the necessary samples for laboratory examination (blood, stool, and any other specimen that might be needed) and to complete all clinical evaluations while minimizing the stress the child must bear.

All 20 Italian adoption-focused centers follow the *ad hoc* GLNBI diagnostic and aiding protocol, in order to identify infectious diseases, nutritional deficiencies, immunization status, intestinal parasitosis, or other pathologies. These can be found in [30], [31], and [32].

From 1st January 2002 to 31st December 2017 data of all children evaluated by the *San Vito al Tagliamento* GLNBI Center was collected. Data regarding date of birth, sex, birthplace, arrival date in Italy, date of the first visit at our clinic and any possible health certificate they might have carried along were recorded for each child

(family history, past and recent medical history, any previously performed laboratory test, vaccine certifications, *etc.*. .) (see [18]).
Laboratory blood tests included serological research of vaccine immunization (Diphtheria, Tetanus, Pertussis, Poliomyelitis, Rubella, Mumps and Measles), serological tests for ongoing or previous infections with HIV (both 1 and 2), Syphilis via TPHA, HBV, HCV, blood count, erythrocyte sedimentation rate (ESR), serum protein electrophoresis, and dosing of blood sugar levels, creatinine, transaminase, ferritin, calcium, magnesium, phosphorus, alkaline phosphatase, vitamin D, and parathormone.
Moreover, Mantoux test (PPD), aiming to evaluate any ongoing or previous tubercular infection, microbiological test on fecal samples for parasitological investigation, clinical urine tests, and thyroid hormone levels were performed.
Along with these laboratory tests, a complete physical examination for assessing the child's overall health status was performed and, when facing potential specific pathologies, a specialist's visit (pediatric orthopaedist, dermatologist, otorhinolaryngologist, endocrinologist, surgeon, ECG, echocardiogram, *etc.*. .) was prescribed.

A statistical evaluation of the collected data was conducted; *p–value* <0.05 was considered statistically significant. For more information on the statistical tests we employed, please see Section 2.5.

Ethics committee approval This study was approved by the ethics committee of the *Burlo Garofolo Children's Hospital*, before beginning, and was conducted always bearing in mind the children's best interest.

2.1 The aim of this study

This study aimed to elaborate on the multitude of data this screening protocol provides, to understand and evaluate whether there might be space for simplification, revision, or stratification in the considered procedures. Over 17 years data was collected from every single child, in order to further uncover which diseases affect these children and what can we do to treat them and to prevent short and long-term complications. Moreover, our research group, under the motto "*Simplification*

through knowledge", aimed at looking for every test and procedure that could be questioned and may be halted, so to polish and refine the protocol at its finest. This was made through two main strategies: a profound re-evaluation of the meaning and reason of every test (see Section 4.2), and the research for statistical correlations amongst parameters (discussed in Section 4.3).
This approach was based on two major assumptions (or beliefs, if you will):

1. Internationally adopted children, despite their young age, have already endured hardships that most us, writers and readers can only imagine. Thus, we believe that their place is at home with their own new families, not in hospital beds. We think that, if our work even only reduces by one the number of total blood test tubes that are drawn from these children, we would feel satisfied.
2. We believe that medicine should be "*simplified through knowledge*": tests should strictly be ordered only if their outcome changes your subsequent operative choices.

2.2 The population in exam

285 internationally adopted children were evaluated from January 1^{st}, 2002 to December 31^{st}, 2017; 102 were female (36.17%) and 180 male (63.83%). The three missing children are due to their sex never being registered in the dataset. The mean (m) age at the time of evaluation was 5.2 years (67.8 months), with a standard deviation (σ) of 2.98 years. The age range spanned from 6 to 156 months. Age overlapped in females and males: for the first group, m was 5.53 and σ 3.01; in the latter, m was 5.06 and σ 2.97.
Moreover, children were evaluated approximately two months after their arrival in Italy ($m = 2.23$ and $\sigma = 2.07$).

The study sample was highly representative of the original population since 99.65% (284/285) of the internationally adopted children in Friuli-Venezia Giulia during this period were included. See Section 2.2.1 for more information on the inclusion and exclusion criteria used.

The entire population was divided into four groups, in order to better establish whether geographical origin was a relevant factor in many of the later examined pathologies. Next to each zone, the color used in Figure 2.1 to represent it, is included. The four areas were:

1. **Africa** 🟧, including:
    - Benin
    - Burkina Faso
    - Congo
    - Ethiopia
    - Ghana
    - Guinea Bissau
    - Ivory Coast
2. **Asia** 🟪, including:
    - Armenia
    - China
    - India
    - Nepal
    - Philippines
    - Siberia
    - Sri Lanka
    - Vietnam
3. **Eastern Europe** 🟥, including:
    - Albania
    - Bulgaria
    - Hungary

- Moldavia
- Romania
- Russian Federation
- Ukraine

4. **Latin America** 🟦, including:
    - Brazil
    - Colombia
    - Costa Rica
    - Guatemala
    - Peru

The study sample grew year after year, as shown in Figure 2.1. In particular, it increased rapidly between 2002 and 2010; after that, the total number of children brought to the center's attention stabilized (more or less) for the rest of the study, until its end, in 2017.

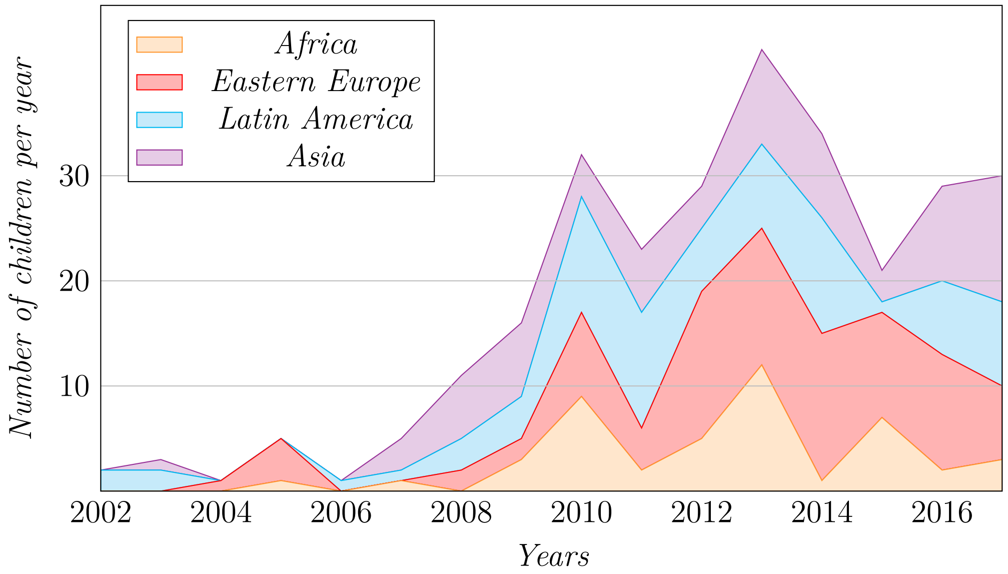

Figure 2.1: Our population's origin distribution by year. Total of children visited via the screening protocol, stratified by geographic area of origin.

2.2.1 Inclusion and exclusion criteria

All internationally adopted children brought to the *San Vito al Tagliamento* GLNBI Center for medical attention, who underwent the GLNBI diagnostic and aiding protocol in the considered period, were included in the study. Only three children were excluded, due to the lack of information, because of voluntary early withdraw from the screening protocol.

The choice for so broadly defined inclusion criteria was made on the explicit intent of the study: describing, as truthfully as possible, the health status of international adoptees. Therefore, the study group had to be as similar as possible to the population under exam. Moreover, this was meant to be a descriptive study, so the risk for confounders was deemed limited, allowing us to consider the close-to-be entirety of the examined children.

As expressed in Section 2.2, we consider our study group to be highly representative of the population in exam: international adoptees.

2.3 The dataset

For the dataset, Microsoft Excel (Version 16.17) was chosen as the database environment, because of its widespread use and its gentle learning curve. The program ran on an early 2015 MacBook Pro with the operating system MacOS High Sierra (version 10.13.6), 64 bit.

The data was collected on an Excel spreadsheet during the years, usually twice per year, during the whole study period. The physicians working at San Vito al Tagliamento GLNBI Center meticulously inserted the children's information in the dataset.

In the Introduction to Appendix A, on page 50, Table A.1 portrays the spreadsheet's full column-parameter correspondence, including units of measurement or cell type and a short description.

2.4 Dataset elaboration

At this point, it should be clear how data were collected, from which population of patients, and how this data was stored. In the following sections, it will be explained how the data was handled in order to produce the results illustrated in Chapter 3 on page 31. In particular, specific expressions were set up in the Excel spreadsheet via the VBA programming language, in order to understand which registered values were pathological and which were not (see Section 2.4.1). In Section 2.4.2 it will be explained how and which cut-off values were chosen for this study and later implemented in the dataset elaboration. Lastly, in Section 2.4.3, particular mention will be made on gastrointestinal parasites.

2.4.1 VBA expressions

In order to allow for a precise statistical analysis, the dataset had to be tuned for this purpose. This was achieved via the implementation of VBA expressions in the Excel spreadsheet in *ad hoc* columns. In particular, these little snippets of code were used to understand whether a specific value was pathological or not. This method was applied to:

- Age in years (in Section A.1)
- Geographic area of origin (in Section A.2)
- Weight and height (in Section A.3.1)
- Haemoglobin (in Section A.3.2)
- MCV (in Section A.3.3)
- Circulating iron (in Section A.3.4)
- Ferritin (in Section A.3.5)
- Vitamin D (in Section A.3.6)

- Parasitic infections and their groupings (in Sections A.4, A.4.1, and A.4.2)

An explained overview of all the employed expressions can be found in Appendix A on page 50.

2.4.2 Cut-off values

At this point, it was necessary to understand which values of each parameter were to be considered positive, negative or anything in between. Therefore, cut-off values were established via extensive research of the most recent medical literature. Every parameter will be now discussed on its own in the following sections.

2.4.2.1 Height and Weight

According to [33], [34], and [35] height and weight are fundamental parameters to appropriately establish whether a child is generically ill since many infancy diseases disturb statural and ponderal growth; they can alter the first, the latter or both axes. We decided to focus on height and weight mainly as markers of malnutrition or chronic systemic disease.

Despite medical literature being unanimously decisive on setting the cut-off for both height and weight at the 3rd percentile (see [33], [36], and [37]), we decided to consider pathological values under the 10th percentile instead. We preferred losing on some specificity but ensuring the best sensibility, rather than the opposite. Precisely measuring a child may be a hard task, and growth curves may not always be coherent with one another, so we preferred to stick to *"better safe than sorry"*.

2.4.2.2 Haemoglobin

Any physician knows that determining whether a haemoglobin value is pathological or not is impossible without any other knowledge of the patient's demographic information, physiological state, recreational habits, *etc.*... The primary factors that modulate haemoglobin serum levels are the following:

1. Age: main one when studying a pediatric population.
2. Sex: not relevant in pediatric age.
3. Altitude: wasn't considered in our study, because of the impossibility of retrieving such a piece of information from adoption records.

Therefore, we elaborated the scheme illustrated in Table 2.1, based on the World's Health Organization (WHO) international 2017 guidelines. These can be found at [38]. As briefly explained above, not having to consider sex or altitude made studying anemias much easier.

		Anemia[1]		
Population	Non-anemia[1]	Mild[2]	Moderate	Severe
Children 6-59 months of age	$\geqslant 110$	$100 - 109$	$70 - 99$	$\leqslant 69$
Children 5-11 years of age	$\geqslant 115$	$110 - 114$	$80 - 109$	$\leqslant 79$
Children 12-14 years of age	$\geqslant 120$	$110 - 119$	$80 - 109$	$\leqslant 79$
Non-pregnant women	$\geqslant 120$	$110 - 119$	$80 - 109$	$\leqslant 79$
Pregnant women	$\geqslant 110$	$100 - 109$	$70 - 99$	$\leqslant 69$
Men	$\geqslant 130$	$110 - 129$	$80 - 109$	$\leqslant 79$

TABLE 2.1: Employed haemoglobin cut-off values.

Source: World's Health Organization international 2017 guidlines for the diagnosis and treament of anemia (see [38])

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[1] All haemoglobin values are expressed in g/l.

[2] *Mild* is a misnomer: iron deficiency is already advanced by the time anemia is detected. The deficiency has consequences even when no anemia is clinically apparent.

Therefore, based on haemoglobin serum levels, children were stratified as affected with the following conditions:

1. Non-Anemia
2. Anemia
    - Mild[2]
    - Moderate
    - Severe

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.3.2 on page 56.

2.4.2.3 MCV

The Mean Corpuscular Value (MCV) was used in order to identify primarily genetic diseases (β-thalassemia minor) and carential states (iron, vitamin B_6 and B_{12} deficiencies). In particular, it allowed us to separate macrocytic and microcytic anemias. The mean physiological value for MCV depends on numerous factors:

1. Sex
2. Age
3. Alcohol and nutritional intakes
4. Haematopoietic functionality and distribution of haemoglobin variants
5. Endocrinological disorders (*a.e.* hypothyroidism)
6. Chronic intoxication (*a.e.* lead poisoning)
7. Consumption of many different medications (*a.e. colchicine, heparin, estrogens, phenytoin, nitrofurantoin, triamterene,* and *trimethoprim*)

Therefore we based our cut-off values for MCV on a recent review published on the *International Journal of Laboratory Hematology* (see [39]), which evaluated these parameters in a pediatric population. Table 2.2 summarizes how these values were distributed. It also shows cut-off values for ferritin, because the same review was the source for that parameter as well.

	Female		Male	
Age	Ferritin[3]	MCV[4]	Ferritin[3]	MCV[4]
0-4 years of age	8–82	69–85	9–85	71–85
5–9 years of age	11–99	75–89	12–94	76–88
10–14 years of age	8–94	78–92	14–84	76–90
15-19 years of age	6–109	77–94	20–191	78–93
20-24 years of age	7–129	78–95	35–318	82–94

Table 2.2: Employed MCV cut-off values.

Source: Åsberg et al. on International Journal of Laboratory Hematology (see [39])

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.3.3 on page 58.

2.4.2.4 Ferritin

Serum ferritin dosage is a direct marker of the patient's iron storage status. Thus, we recorded its value to understand the etiologic nature of anemias in our population further. The employed cut-off values can be found in Table 2.2 and are expressed in ng/ml.

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.3.5 on page 61.

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[3] All ferritin values are expressed in ng/ml.

[4] All MCV values are expressed in fl.

2.4.2.5 Circulating Iron

The serum circulating iron value was defined as regular if it belonged to the interval 16–129µg/dl, extremes included. This parameter was considered just as a countercheck for establishing the patient's iron storage status, that we deduced from serum ferritin.

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.3.4 on page 61.

2.4.2.6 Vitamin D

Vitamin D deficiency and insufficiency constitute a significant health issue in internationally adopted children, as explained in Section 1.2 on page 10, 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. Thus, we dosed serum levels of calcifediol, also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D (abbreviated $25(OH)D$).
Recent literature has recently openly discussed how vitamin D deficiency should be defined, especially in pediatric age, and therefore what we should consider a healthy intake. The general international consensus states that to define Vitamin D serum cut-off values (intended as 25-hydroxyvitamin D), alkaline phosphatase and calcium serum levels should be taken into acquaintance so to determine a healthy bone development, ignoring the now well-known vitamin D extra-skeletal effects. The strongest recommendation for this comes from 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 [40]. Moreover, [41], a statistically reliable and recent Italian review on a pediatric population, supports this statement, just as the reports in [42] and [43].

Table 2.3 summarizes the cut-off values, resulting from this approach. Since vitamin D serum levels are variably expressed both in ng/ml and nmol/l, both have been included in the following table. For this study, ng/ml were used because this unit of measurement was the one used by our laboratories.

Unit of Measurement	Sufficiency	Insufficiency	Deficiency	Severe Deficiency
ng/ml	$\geqslant 20$	19–10	9–4	$\leqslant 3$
nmol/l	$\geqslant 50$	49–25	24–10	$\leqslant 9$

TABLE 2.3: Employed Vitamin D cut-off values.

Source: Saggese G et al. in "Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians" (see [41])

Based on our laboratory findings we, therefore, scored the child's vitamin D status from 0 to 3, dividing their serum levels in:

- Sufficient
- Insufficient
- Deficient
- Severely Deficient

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.3.6 on page 62.

2.4.3 Parasites grouping

Gastrointestinal infestations are a common disease in internationally adopted children, as stated in Section 1.2. We found 8 different *genera*, most of them co-infecting the same child. Because of the scarceness of data per *genus*, though, we decided to group them up into two separate groups, in order to increase statistical significance.

The found pathogens are the following:

Group 1: Parasites usually responsible for gastrointestinal bleeding and, therefore, iron-deficient low-ferritin microcytic anemia. These included:

a) Entamoeba
b) Ancylostoma
c) Trichuris

Group 2: Parasites usually responsible for gastrointestinal malabsorption. These included:

a) Giardia
b) Strongyloides
c) Hymenolepis
d) Blastocystis
e) Endolimax

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.4 on page 63.

2.5 Statistical Analyses

The population-describing analyses were conducted using relative frequencies and percentages for categorical variables, and means and standard deviations or medians and inter-quartile intervals for continuous ones. We preferred to use the latter because the scarcity of data prevented us from checking for normal distribution.

Nonparametric tests, such as the *Mann-Whitney-Wilcoxon rank-sum test* or the *Kruskal-Wallis equality-of-populations rank test*, were employed to evaluate the difference between continuous variables in different groups. One analysis or the other was performed based on the number of groups, case by case: if two, the *Mann-Whitney-Wilcoxon* test was used, if more than two, *Kruskal-Wallis* test, instead. To study the relation between two dichotomous variables, or one dichotomous and one

categorical, we used the *two-tailed Fisher's exact test* and, to investigate whether a dichotomous event was associated with one or more independent variables, we preferred using logistic regression.
Lastly, in order to study the correlation between continuous variables, we preferred using *Spearman's rank correlation test*.

All statistical analyses were conducted using the Stata/IC software, version 14.2 (*StataCorp LLC*, College Station, USA).

Chapter 3

Results

In the following chapter, the numerical results of this study will be displayed and explained. This work was accomplished through the priceless collaboration with Dott. Monasta L. The full discussion will be tackled in Chapter 4 on page 44.

3.1 Descriptive analyses

As stated in Section 2.2, 285 internationally adopted children were evaluated from January 1$^{\text{st}}$, 2002 to December 31$^{\text{st}}$, 2017; 102 were female (36.17%) and 180 male (63.83%). The three missing children are due to sex never being registered in the dataset. Boys were numerically dominant in all considered regions (55-79%).
The mean (m) age at the time of evaluation was 5.2 years (67.8 months), with a standard deviation (σ) of 2.98 years. The age range spanned from 6 to 156 months. Age overlapped in females and males: for the first group, m was 5.53 and σ 3.01; in the latter, m was 5.06 and σ 2.97.
Moreover, children were evaluated approximately 2 months after their arrival in Italy ($m = 2.23$ and $\sigma = 2.07$).

The evaluated children came from all over the globe, but mostly from Russia ($n = 71$; 25.09%), India ($n = 43$; 15.19%), Brazil ($n = 36$; 12.72%),and Ethiopia ($n = 33$;

11.66 %). If we were to consider the 4 zones (as defined in Section 2.2), cumulatively, children mostly came from Eastern Europe (n = 90; 31.80%), followed by Latin America (n = 75; 26.50%) and Asia (n = 72; 25.44%); fewer came from Africa (n = 46; 16.25%). Table 2.1 shows the growth of our group's size over the years and where these children came from.

117 children out of 271 (43.17%) had a pathologically underweight, 96 out of 270 (35.55%) were short for their age.

Haemoglobin was found pathologically low in 22 patients out of 280 (7.86%). Among these, 9 were moderate, constituting 40.91% of anemias. Moreover, 9 also presented a pathological MCV and 15 a low ferritin. These findings will be discussed in Section 4.1.

Ferritin was found pathological in 87 out of 251 children (34.66%): most of these cases were mild deficiencies, but 18 (7.17%) were very severe. This data can be found in Table 3.1.

		Ferritin deficiency			
	Absent	Mild	Moderate	Severe	Total
Frequencies	164	41	28	18	251
Percentages	65.34%	16.33%	11.16%	7.17%	100.00%

Table 3.1: Absolute frequencies and percentages of ferritin deficiencies in our population.

As for the immunization status, only 87 (34.25%) showed a completely valid immunization to vaccine-preventable disease. Almost 65% of all children were found to have insufficient antibody levels for at least one of the considered infections. Three children were exposed *entirely*. The following Table 3.2 shows the immunization status, regarded as *complete*, *incomplete* or *absent* for every considered geographical region. Africa resulted being the region with the lowest immunization rate (just over $\sim$ 10%).

	Immunization status			
Region[1]	Absent	Incomplete	Complete	Totals
Africa	2 (5.56%)	30 (83.33%)	4 (11.11%)	36
Latin America	1 (1.47%)	44 (64.71%)	23 (33.82%)	68
Asia	1 (1.47%)	41 (63.08%)	23 (35.38%)	65
Eastern Europe	0 (0.00%)	48 (56.47%)	37 (43.53%)	85

Table 3.2: Absolute values and percentages of immunization status of our population, divided by region.

Out of 285 examined children, on 180 vitamin D serum levels were tested: 60 (33.33%) were defined deficient, 12 (6.67%) insufficient, and no children were found to be severely insufficient. Only 108 (60%) had sufficient (and therefore acceptable) vitamin D intake. Most of the children who suffered insufficiency were Asian ($8/12 \simeq 66.66\%$).

The *Kruskal-Wallis equality-of-populations rank test* was performed in order to verify if there were any statistically significant differences in vitamin D mean serum levels between our four zones. Its results were on the limits of statistical significance (*p-value* = 0.0524). Table 3.3 shows the number of considered cases (n), mean serum levels of vitamin D (m) and standard deviation (σ) in each considered region.

Region[2]	n	m	σ
Asia	43	19.64	9.05
Eastern Europe	68	23.74	10.13
Latin America	39	24.20	5.87
Africa	30	24.33	9.58

Table 3.3: Mean vitamin D serum levels and relative standard deviation in each region in our population.

During our analysis, six countries presented extremely low mean vitamin D serum levels; they are listed in Table 3.4, alongside the number of considered cases per country and the standard deviation.

---

[1] Regions were ordered by the ascending percentage of complete immunization status.

[2] Regions were ordered by the ascending mean levels of serum vitamin D.

Country[3]	n	m	σ
Ukraine	1	14.00	-
China	9	15.63	7.00
Bulgaria	2	16.00	2.97
Romania	2	16.90	0.57
Hungary	3	17.63	5.29
Benin	1	17.9	-
Vietnam	5	21.1	12.79

TABLE 3.4: Mean vitamin D serum levels and relative standard deviation of the lowest mean vitamin D values in our population.

Parasitic gastrointestinal infections were persistent in our population: 101, out of the total 245 performed tests (41.22%), resulted positive for at least out of considered intestinal parasites (listed in Section 2.4.3). Group 1 parasites were more common in children coming from Latin American and less in Asia; group 2 parasites infected more African children and less Eastern Europeans. None of these results were statistically significant, though: group 1 parasitosis resulted in a 0.105 at the *Fisher's exact test*, group 2 in 0.122. All our data relative to parasitic infections can be found in Table 3.5.

	Group 1		Group 2	
Region[4]	Positive	Negative	Positive	Negative
Asia	11 (17.74%)	51 (82.26%)	13 (20.97%)	49 (79.03%)
Africa	8 (19.51%)	33 (80.49%)	12 (29.27%)	29 (70.73%)
Eastern Europe	16 (21.62%)	58 (78.38%)	9 (12.16%)	65 (87.84%)
Latin America	25 (34.72%)	47 (65.28%)	17 (23.61%)	55(76.39%)
Total	60 (24.10%)	189 (75.90%)	51 (20.48%)	198 (79.52%)

TABLE 3.5: Parasite faecal test result, both as frequencies and as percentages, divided per region.

---

[3] Countries were ordered by the ascending mean levels of serum vitamin D.

[4] Regions were listed in alphabetical order.

Out of 273 performed Mantoux tests, 46 (16.84%) resulted positive: a considerable amount. Table 3.6 displays all the data on this matter, again, divided by region. Eastern Europe and Africa (as one would expect) resulted in being the regions with the highest percentage of positive cases. A *Fisher's exact test* demonstrated a positive statistical correlation between Mantoux test positivity and area of origin ($p{<}value = 0.002$).

	Mantoux test result		
Region[5]	Positive	Negative	Total
Eastern Europe	22 (25.29%)	65 (74.71%)	87 (31.87%)
Africa	10 (21.74%)	36 (78.26%)	46 (16.85%)
Asia	11 (15.94%)	58 (84.06%)	69 (25.27%)
Latin America	3 (4.23%)	68 (95.77%)	71 (26.01%)
Total	46 (16.85%)	227 (83.15%)	273 (100.00%)

Table 3.6: Mantoux test results and relative percentages in each region.

The *two-sample Mann-Whitney-Wilcoxon rank-sum test* was performed on each region between Mantoux test results and mean age in the positive and negative groups. It returned a statistically significant ($p{>}|z| = 0.028$) result only for Asia: positive Asiatic children had a mean age of 85 month ($\sigma = 31.61$), negative 62 months ($\sigma = 37.56$). We believe that with bigger sample sizes, this would be found true for Latin America as well.

Figure 3.1 below portrays our population's age distribution (in months) stratified by our four zones and Mantoux test results, perfectly representing this conclusion.

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[5] Regions were ordered by the descending percentage of positive tests.

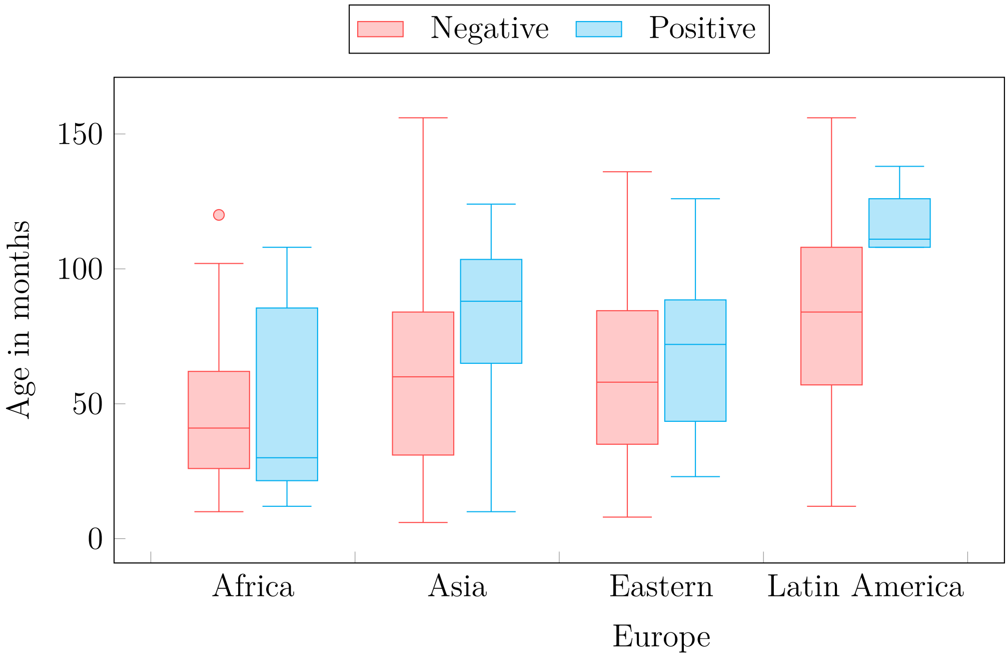

Figure 3.1: Boxplot of our population's age distribution (in months) stratified by our four zones and Mantoux test results.

Concerning other infectious diseases, no patients were found positive to hepatitis C antibodies out of the 282 tested, 4 were positive for hepatitis B superficial antigen (HBsAg) out of 281 (1.42%), only one child was HIV-positive out of 282 (0.35%), and just one was positive for syphilis via TPHA, out of 256 (0.39%) performed tests.

3.2 Analyzing the costs

Health care is a huge worldwide industry, worth billions, and, as such, must undergo market rules. Thus, we decided to analyze the costs, both of the whole screening protocol and of each test. All the needed data was found in the 2018 *Nomenclatore tariffario di specialistica ambulatoriale* of Friuli-Venezia Giulia (which can be found in [44]).

	Test	Cost[6]
	Blood sugar levels	1.20 €
	Creatinine	2.00 €
	Blood count	5.30 €
	Alkaline phosphatase	2.20 €
	Calcium	8.00 €
	Phosphorus	2.10 €
	Transaminase	1.90 €
	Ferritin	13.90 €
	ESR	1.20 €
	$HCVAb$	28.40 €
	$HBsAg$	11.40 €
	$TPHA$	7.20 €
	$HIV_{1,2}Ab$	13.20 €
	3 Parasitic microscopic exam	13.50 €
	Clinical urine tests	3.00 €
	Mantoux test (PPD)	7.00 €
	Serum protein electrophoresis	7.00 €
	Vitamin D	20.30 €
Immunization status	Mumps	11.80 €
	Tetanus	12.70 €
	Diphtheria	12.70 €
	Morbillo	8.40 €
	Measles	5.20 €
	Pertussis	8.20 €
	Poliomyelitis	6.50 €
	Type B Haemophilus	5.20 €
	HBsAb	13.20 €
Total		232.70 €

TABLE 3.7: Cost of all performed test, as defined by the *GNLBI protocol.*

Source: Nomenclatore tariffario di specialistica ambulatoriale of Friuli-Venezia Giulia (see [44]).

The total cost of the screening panel is 232.70 € per child, who undergoes the full set of tests. In Section 4.2 on page 45 of this thesis, an overview of these tests' rationale will be presented. We believe that some may not be so worthwhile, because they do not change the operative course of these children or because they lack too much specificity to be worth including.

3.3 Statistical inference of data

Statistical inference was one of the main focus points of this study. As explained in 2.1, the research for correlations amongst the considered variables is considered to be one of our most relevant objectives, because it could have meant spare some hospitalization time and some invasive tests from the children brought to our attention, achieving benefits on an economical, health and comfort level.

First of all, we investigated vitamin D deficits. It was reasonable to us that vitamin D serum levels were correlated to iron-deficient anemias, because of their shared natures as deficiency states. Therefore we ran *Spearman's rank correlation test* on haemoglobin and vitamin D values, which resulted in the two variables being independent ($p > |t| = 0.3086$). This result was later confirmed by performing a *Fisher's exact test* ($p = 0.082$). The results were plotted in Figure 3.2 and summarized in Table 3.8.

---

[6] All the reported costs are in Euros (€).

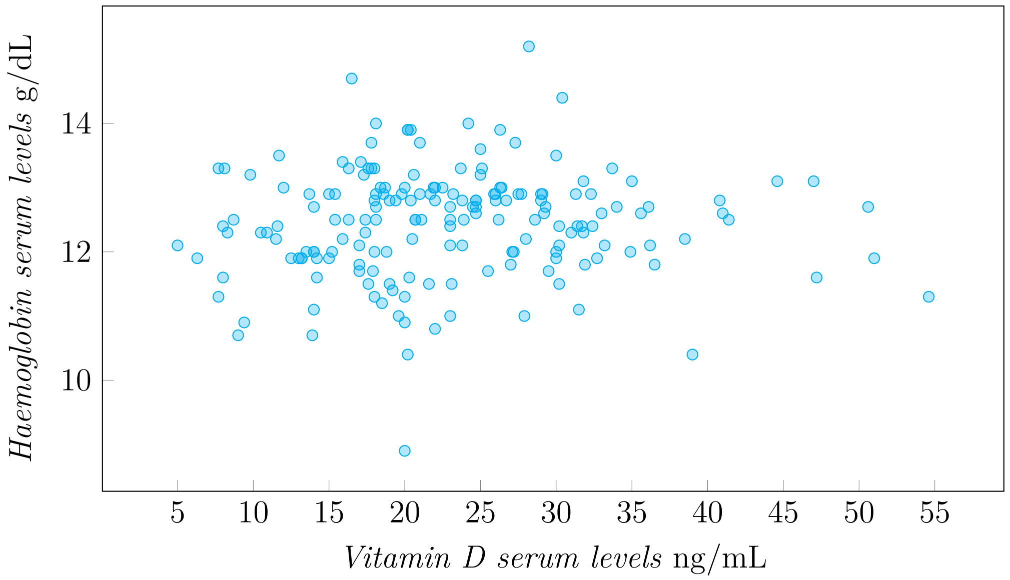

FIGURE 3.2: Scatter plot of Vitamin D and Haemoglobin serum levels.

		Anemia			
		Absent	Mild	Moderate	Total
Vitamin D deficiency	Absent	102 (56.66%)	4 (2.22%)	2 (1.11%)	108 (60.00%)
	Mild	58 (32.22%)	2 (1.11%)	0 (0.00%)	60 (33.33%)
	Moderate	10 (5.56%)	0 (0.00%)	2 (1.11%)	12 (6.67%)
	Total	170 (94.44%)	6 (3.33%)	4 (2.22%)	180 (100.00%)

TABLE 3.8: Frequencies and percentages of anemic and vitamin D deficient children in our population.

Moreover, we tried to correlate vitamin D serum levels with ferritin as well: *Spearman's rank correlation test* was performed again, and it confirmed the independent nature of these variables ($p > |t| = 0.2734$). This result was later confirmed by performing a *Fisher's exact test* ($p = 0.220$). Figure 3.3 and Table 3.9 show these results.

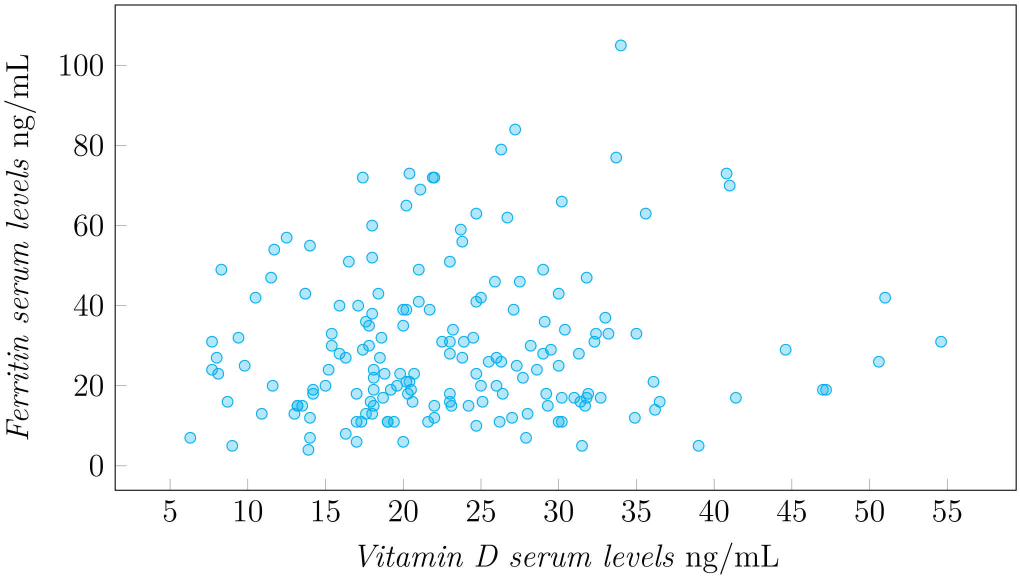

FIGURE 3.3: Scatter plot of Vitamin D and Ferritin serum levels.

		Ferritin deficiency				
		Absent	Mild	Moderate	Severe	Total
Vitamin D deficiency	Absent	68 (39.53%)	23 (13.37%)	10 (5.81%)	4 (2.33%)	105 (61.05%)
	Mild	32 (18.60%)	11 (6.40%)	10 (5.81%)	4 (2.33%)	57 (33.14%)
	Moderate	7 (4.07%)	1 (0.58%)	0 (0.00%)	2 (1.16%)	10 (5.81%)
	Total	107 (62.21%)	35 (20.35%)	20 (11.63%)	10 (5.81%)	172 (100.00%)

TABLE 3.9: Frequencies and percentages of ferritin and vitamin D deficient children in our population.

Then, we further studied anemias, by running a *logistic regression*. Anemia was considered as a dichotomous variable (a child either was anemic, or he wasn't), and so was done for parasitic infections, MCV, and ferritin serum levels. We found that anemia is negatively correlated with MCV levels ($z = -3.18$, $p > |z| = 0.001$ with a $CI_{95\%} = [0.75, 0.93]$). This consideration visibly stands out in Table 3.10. Out of 22 anemias, 9 alongside a pathological MCV ($\sim 41\%$); on the other hand, only 11% of non-anemic children presented a pathological MCV value.

Statistical analyses did not highlight any other statistically relevant correlations amongst the considered variables, listed above.

		Anemia		
		Absent	Present	Total
MCV	Normal	228 (82.31%)	27 (9.75%)	255 (92.06%)
	Pathological	13 (4.69%)	9 (3.25%)	22 (7.94%)
Total		241 (87.00%)	36 (13.00%)	277 (100.00%)

TABLE 3.10: Frequencies and percentages of children presenting anemia and low-MCV in our population.

Because of this strong correlation between low-MCV and low-haemoglobin, we decided to consider as one the population with these two parameters offset (3.25% of all studied cases) and try to find out more about the etiological nature of this anemic state. We found that there was a positive correlation between low ferritin serum levels and low-MCV anemia, confirming the high prevalence of iron-deficiency in our population. This was established at the *Fisher's exact test* ($p = 0.001$). Table 3.11 shows our data concerning these considerations.

This low-MCV low-haemoglobin population originated entirely from Asia ($n = 5$, $\sim 55\%$) and Eastern Europe ($n = 4$, $\sim 44\%$). This was statically significant, with a Fisher's exact test result of $p = 0.033$. In particular, the only involved countries were India ($n = 5$, $\sim 55\%$), in Asia, and Russia ($n = 2$, $\sim 22\%$) and Bulgaria ($n = 2$, $\sim 22\%$), in Eastern Europe.

		Low-Hb and Low-MCV		
		Absent	Present	Total
Ferritin	Normal	162 (65.32%)	1 (0.40%)	163 (65.73%)
	Pathological	77 (31.05%)	8 (3.23%)	85 (34.27%)
Total		239 (96.37%)	9 (3.63%)	248 (100.00%)

TABLE 3.11: Frequencies and percentages of children presenting pathological ferritin in the anemic low-MCV population.

Moreover, we tried to take a closer look at anemias and parasitic infections: the variables were found still to be independent at *Fisher's exact test* ($p = 0.935$). No correlation was found (leaving us pretty surprised) neither between anemia and group 1 and 2 gastrointestinal infestations, with a *Fisher's exact test* result of $p = 0.205$ and $p = 0.669$ respectively. Tables 3.12a, 3.12b, and 3.12c summarize our findings.

On the other hand, we found a positive correlation between pathological ferritin and group 1 parasitic infection, with a *Fisher's exact test* result of $p = 0.003$. This finding is in accordance with our definitions of group 1 and 2 parasites since the first commonly express their infections through gastrointestinal bleeding.

		Anemia			
		Absent	Mild	Moderate	Total
Parasitic infection	Absent	130 (53.50%)	7 (2.88%)	5 (2.06%)	142 (58.44%)
	Present	94 (38.68%)	4 (1.65%)	3 (1.23%)	101 (41.56%)
	Total	224 (92.18%)	11 (4.53%)	8 (3.29%)	243 (100.00%)

(A) Frequencies and percentages of anemia and parasitic infections in our population.

		Low-Hb Low-MCV		
		Absent	Present	Total
Parasitic infection	Absent	176 (72.13%)	8 (3.28%)	184 (75.41%)
	Present	60 (24.59%)	0 (0.00%)	60 (24.59%)
	Total	236 (96.72%)	8 (3.28%)	244 (100.00%)

(B) Group 1 infestations

		Low-Hb Low-MCV		
		Absent	Present	Total
Parasitic infection	Absent	188 (77.05%)	6 (2.46%)	194 (79.51%)
	Present	48 (19.67%)	2 (0.82%)	50 (20.49%)
	Total	236 (96.72%)	8 (3.28%)	244 (100.00%)

(C) Group 2 infestations

TABLE 3.12: Frequencies and percentages of parasitic infected and anemic children in our population.

Lastly, we tried a *logistic regression* on low height-for-age, anemia, group 1 and 2 parasitic infections, Mantoux test results, and vitamin D serum levels, but no statistically relevant effect was found. We believe that through a bigger sample size anemias, Mantoux test results, and group 2 parasitic infections would have found a rather strong correlation with pathological height-for-age, as an indicator of chronic illnesses in the child.

Chapter 4

Discussion

In the following and last chapter of this thesis, the results presented in Chapter 3 will be discussed. We'll focus on describing the most common diseases among internationally adopted children (in Section 4.1), analyzing which tests are in our opinion worthwhile amongst the ones listed in the GNLBI protocol (in Section 4.2), and lastly present our conclusions on the most relevant statistical correlations we found (in Section 4.3).

4.1 Health status of internationally adopted children

We found that statural and ponderal delayed growth are relatively common among international adoptees. These alterations are probably complex and multifactorial. We did not find statistical evidence for any possible cause, but we believe that FASD (that wasn't considered in this study), malnutrition, anemia, tuberculosis, and parasitic gastrointestinal infections are the most likely significant factors in determining this growth delay. Literature shows that these children are *late bloomers* and they will grow up to their range height and weight during adolescence.

Then, anemia was found to be another common condition. It resulted linked to iron-deficiency for the most part, enforcing the need for iron supplements. The other leading cause is β-thalassemia minor, which strongly requires serum protein electrophoresis, alongside a complete blood count. On the other hand, our study evidenced that parasitic gastrointestinal infections, despite being highly frequent, are not a common cause of anemia in internationally adopted children, as instead modern literature and common knowledge would suggest.

As for the immunization status, this often offers incomplete protection from vaccine-preventable diseases (65% of all children) and, therefore, it should be strongly advised to screen all internationally adopted children for their immunization status at their arrival in each country of destination. We concur with international guidelines that pre-adoptive immunization records may not be assumed as truthful or correct.

Moreover, vitamin D serum levels are commonly deficient or insufficient in international adoptees (40%). This consideration strongly reinforces the need for vitamin D prophylaxis in this unique population, perhaps even without testing for vitamin D status, if the clinical evaluation that suggest rickets.

Lastly, infectious diseases are common among international adoptees, but these are rarely severe: HIV, HBV, HCV, and syphilis are almost never present: 1, 4, 0 and 1 cases respectively in our 17-year-spanning study. On the other hand, latent tuberculosis (16.84%) and parasitic gastrointestinal infection (41.22%) are relatively common.

In the following Section 4.2, we'll present our recommendations in light of these new findings.

4.2 Is everything we do worthwhile?

The *GLNBI diagnostic-aiding protocol* (found in [31]) is a milestone for adoption-specialized pediatricians. Although it's thorough and complete, it may be too extensive for a universally applied screening protocol, and not all of the recommended tests and examinations are useful from a cost-benefit perspective. In particular, some sections do not directly influence the operative clinical path the child must follow and are therefore suppressible. Others, on the other hand, have a powerful impact on the child's health and strongly influence the further development of the child's clinical plan.

In the following Sections 4.2.1 and 4.2.2, our considerations about the different segments of the protocol will be presented, alongside our recommendations.

4.2.1 What we believe to be worthwhile

First of all, performing a complete blood count is one of the most useful laboratory tests, from a cost-benefit perspective. The measurement of MCV, ferritin serum levels, and of the distribution of serum protein via electrophoresis completes the evaluation of anemia and its most frequent etiologies. These tests are necessary, and pediatricians should be strongly advised towards performing them as soon as possible in internationally adopted children.
In our study, 280 blood counts and 243 serum protein electrophoresis were performed, 251 serum ferritin levels were tested. These cost respectively: 5.30 €, 7.00 €, and 13.90 €. Total costs amount to 1484.00 €, 1701.00 € 3488.90 € respectively. The grand total amounted to 6,673.90 € for a complete evaluation of anemic states. We believe this to be a reasonable expense because of the high impact it has on the child's diagnostic and (especially) therapeutic operations.

As explained in Section 3.1 on page 31, the immunization status is long from acceptable in immigrant children: 65% of our population resulted not entirely protected from vaccine-preventable diseases. Modern medical literature hasn't settled yet whether it's best to presume the child not be vaccinated at all and repeat all shots according to the national vaccination calendar, or to test for individual antibody serum levels and perform vaccinations if and only for the ones that show inadequate serum antibody titers. We prefer the second approach because it spared the child of useless injections.
Each immunization status panel costs 70.70 €, and we performed a total of 224

panels, for a total cost of 15.836,80 €. This set of tests is clearly costly, but so are vaccinations. Thus, we assume this is a favorable expense, even if no calculations were performed to determine which approach would better employ resources.

Another critical exam is tuberculosis testing via the Mantoux intradermal reaction test. This is performed by injecting PPD in the dermis (or corium) of the child and waiting for a local flogistical response in the next 24/48 hour period. This is the cheapest way of testing for tubercular exposition since a dose of PPD only costs 7.00 €. We performed 273 Mantoux tests of the years for a total cost of 1,911.00 €: a low-priced evaluation immediately directing the patient to a chest X-ray or at home.

A complete overview of the tests' costs can be found in Table 3.7.

4.2.2 And what may not be

Vitamin D deficiency and insufficiency are common among international adoptees. We tested 180 vitamin D serum levels (20.30 € each), and 72 turned out positive (40%). Since vitamin D supplementation is harmless and that a three-month therapy period costs less than the single test, we advise towards eliminating the test from the screening protocol and administer cholecalciferol (vitamin D_3) to all internationally adopted children for three months in prophylaxis dosage.

Similarly to vitamin D, testing for parasitic infections could be labeled as redundant. All children are administered a dose of *mebendazole* and one of *tinidazole* just after the stool samples are collected. This is an approach we support, but it relegates parasite stool research to a test out of mere curiosity and should, therefore, be abandoned.

In our study, we performed 243 tests for parasites, of which 90 resulted positive, but none of these changed the children's therapeutical future since they were administered doses of *antihelmintic* drugs both if the test ended up positive or not. Each test costs 13.50 € and its removal from the protocol would have saved a total of 3,240.00 €.

Since testing for HCV, HBV, syphilis via TPHA, and both genotypes of HIV resulted in little to no actual pathological evidence, we suggest that these exams shouldn't be included in early screening, due to the inconsistency of their benefits. Instead, they should be performed only if clinical examination points towards such infections or anamnestic risk factors are identified.
We performed 215 tests for HBV, 282 for HCV, 256 for syphilis, and 282 for HIV. 18,818.40 € would have been saved, if these analyses had been performed only on positive children.

4.3 Seeking for support: building correlations

As explained in Section 3.3 on page 38, we firmly believed in the need for reliable results from statistical inference, and, therefore, this was one of the main focus points of this study. As explained in Section 2.1, the research for correlations amongst the considered variables could have meant spare some hospitalization time, and some invasive tests from the children brought to our attention, achieving benefits on an economical, health and comfort level.

Most of our findings in revolved around anemia.

1. **Anemia and MCV**. This correlation enforces the knowledge of the high prevalence of iron-deficient anemia. The leading causes are malnutrition and insufficient iron daily intake, and chronic gastrointestinal bleeding. The last option that must be considered in internationally adopted children is β-thalassemia minor.

2. **Low-MCV anemia and ferritin**. This correlation strengthens, even more, the need for acknowledgment of the high prevalence of iron-deficient anemia. Moreover, it boldly calls for iron supplement-based therapy or prophylaxis in the internationally adopted child.

3. **Low-MCV anemia and country of origin**. Regarding iron-deficient anemia, special attention should be paid to children coming from the Russian Federation and Bulgaria, in Eastern Europe, and India, in Asia.

4. **Ferritin and group 1 parasite gastrointestinal infection**. This finding justifies the need for parasite grouping and the little need for them to be considered *genus* by *genus*.

4.4 Objectives achieved

In Section 2.1 on page 17, the aim of the study was presented. These were achieved over a period of seven months. We evaluated the most common diseases among internationally adopted children, found which tests could be overabundant and found useful correlations that stress the strongest urges of internationally adopted children.

4.5 Future work

Despite us believing that many goals set for this study have been achieved, we also think that future work can be done in order to accomplish a better understanding of this particular pediatric population. Other studies with a larger population under exam could highlight correlations we weren't able to find. In particular, low height-for-age, *genus*-specific parasitic infections, and tuberculosis seem to have space for improvements in their diagnostic and therapeutic processes.

Moreover, the establishment of a national database could be the next step taken to allow all 20 Italian GLNBI Centers to contribute to further study which pathologies affect these children. National and international policies continuously alter infectious diseases' epidemiology, thus dedicated and constant surveillance is mandatory, in order to allow at least some degree of plasticity of decisional and effective practices.

Appendix A

Dataset elaboration: VBA expressions

This appendix provides the full code used in this thesis to elaborate the dataset. Visual Basic for Application (VBA) is the programming language chosen for this purpose, as the most effective and manageable way of refining data in Excel spreadsheets. Further information can be found throughout this thesis, especially in Section 2.4 on page 22 and cut-off values, parameter by parameter, can be found at Section 2.4.2.

In the following appendix, cells are identified by a combination of a letter (identifying the column) and a number (identifying the line), as they initially 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 the following Table A.1.

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

---

[1] Although 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 dataset got larger through the years.

R	Ferritin	ng/ml	Amount of circulating ferritin. This was used to confirm iron-deficiency anemia.
S	Pathological ferritin	*boolean*	Is the $R-field$ low or not?
T	Feces	*text*	List of microorganisms found in triple direct microscopical exams on three fecal samples. The "*negative*" string was used to indicate negativity to all examinations.
U	*Group 1* parasites	*boolean*	Is the $T-field$ positive for one of the following parasites?
V	Entamoeba	*boolean*	Is the child infected with *Entamoeba*? This parasite belongs to *Group 1*.
W	Ancylostoma	*boolean*	Is the child infected with *Ancylostoma*? This parasite belongs to *Group 1*.
X	Trichuris	*boolean*	Is the child infected with *Trichuris*? This parasite belongs to *Group 1*.
Y	*Group 2* parasites	*boolean*	Is the $T-field$ positive for one of the following parasites?
Z	Giardia	*boolean*	Is the child infected with *Giardia*? This parasite belongs to *Group 2*.
AA	Strongyloides	*boolean*	Is the child infected with *Strongyloides*? This parasite belongs to *Group 2*.
AB	Hymenolepis	*boolean*	Is the child infected with *Hymenolepis*? This parasite belongs to *Group 2*.
AC	Blastocystis	*boolean*	Is the child infected with *Blastocystis*? This parasite belongs to *Group 2*.
AD	Endolimax	*boolean*	Is the child infected with *Endolimax*? This parasite belongs to *Group 2*.
AE	Immunization status	*text*	*Complete*, *incomplete* or *negative* immunization statuses on mandatory vaccines in Italy.

AF	HCVab	*boolean*	Is the child positive to hepatitis C antibodies?
AG	HBsAg	*boolean*	Is the child positive to the hepatitis B superficial antigen?
AH	HBVab	*boolean*	Is the child positive to hepatitis B antibodies?
AI	HIV	*boolean*	Is the child positive to HIV antibodies?
AJ	Lue	*boolean*	Is the child positive to syphilis antibodies?
AK	Vitamin D	ng/ml	*25-hydroxycholecalciferol* serum levels.
AL	Pathological Vitamin D	*boolean*	Is $AK - field$ deficient?
AM	Mantoux	*boolean*	Did the Mantoux turn out positive?
AN	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 years)

This VBA expression checks the *Age (in months)* parameter (column C) and, if it's not empty, it divides its value by 12, rounding it down, just as age counting works. This was achieved via the `ROUNDDOWN` function, in order to avoid overestimating children'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 main continents or zones with the following Excel expression. The chosen zones were:

- Africa
- Asia
- Eastern Europe
- Latin America

A more in-depth overview of how geographic zones where dealt with can be found in Section 2.2.

```
=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 dataset contained numerical values of results from many laboratory tests. Cut-off values for these results were established via the most recent literature review, as explained in Section 2.4.2. In the following sections, the code used to determine which of these results where pathological and which were not is displayed and shortly explained.

A.3.1 Weight and height

Height and weight were simple to evaluate since they had already been converted to percentile value. It was enough to compare them to the cut-off value, as follows:

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

A.3.2 Haemoglobin

Haemoglobin required a more complicated and sophisticated expression, in order to be stratified, because haemoglobin pathological cut-offs depend on various factors, as described in Section 2.4.2.2. Moreover mild, moderate and severe anemias had to be differentiated from one another to evaluate the child's health status properly. Each one had an arbitrary value of 1 (*mild*), 2 (*moderate*) or 3 (*severe*) associated with 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
                   )
                )
             )
          )
       )
   );
   ""
)
```

A.3.3 MCV

Just as described for haemoglobin, MCV required more complicated techniques in order to be stratified, because of its variability (through age, sex, *etc.*. . .), as described in Section 2.4.2.3. 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
                  )
               )
            )
         )
      );
      IF(
         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, by merely comparing the result to the normality interval:

```
=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 in *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 in Section 2.4.2.6.

```
=IF(
   AK2 <> "";
   IF(
      AK2 >= 50;
      0;
      IF(
         AND(
            AK2 < 50;
            AK2 >= 25
         );
         1;
         IF(
            AND(
               AK2 < 25;
               AK2 >= 10
            );
            2;
            IF(
               AK2 < 10;
               3
            )
         )
      )
   );
   ""
)
```

A.4 Parasitic Infections

As explained in Section 2.4.3 on page 28, parasites were subdivided into two groups. In the following sections, it's described how this was achieved.

A.4.1 Parasite positivity

Since the *Feces* parameter (column T2) was registered in the dataset as a list of the parasites found positive in the examined stool specimens, we had to proceed with research in this cell. The string `negative` was used when all three analyses resulted negative.
The `FIND` function is a function that, given as argument two strings, returns the number of the starting position of the first text string from the first character of the second text string. On this result, the `IS.NUMBER` function was implemented to test if `FIND` resulted positive and, therefore, returned an integer or not; `IS.NUMBER` returned a boolean (*true* or *false*). This was then integrated into the parasite grouping, as explained in the next Section.
The following VBA expression is the one used for *Entamoebas* (column V):

```
=IF(
   T2 <> "";
   IS.NUMBER(
      FIND(
         "Entamoeba";
         T2
      )
   );
   ""
)
```

This method was used for all the considered pathogens (listed in Section 2.4.3) by changing the first argument of the `FIND` function.

A.4.2 Parasite grouping

To understand whether a child was infected with group 1 or group 2 parasites, a VBA expression was build to check the corresponding cells (V, W and X columns for group 1; Z, AA, AB, AC, and AD for group 2) and check if at least one of them contained a *true* value.

The following expression was used for *group 1* parasites:

```
=IF(
   AND(
      V2<>"";
      W2<>"";
      X2<>""
   );
   IF(
      OR(
         V2;
         W2;
         X2
      );
      1;
      0
   );
   ""
)
```

The following expression was used for *group 2* parasites:

```
=IF(
   AND(
      Z2<>"";
      AA2<>"";
      AB2<>"";
      AC2<>"";
      AD2<>""
   );
      IF(
         OR(
            Z2;
            AA2;
            AB2;
            AC2;
            AD2
        );
        1;
        0
    );
    ""
)
```

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