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Laurea Magistrale in Medicina e Chirurgia

Health Status of Internationally Adopted Children: a Retrospective Study

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"Every single minute matters, every single child matters," every single childhood matters."

- Kailash Satyarthi, Indian children's rights activist

Abstract (Italian)

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Abstract

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Contents

A	bstra	ct (Ita	alian)	ii
\mathbf{A}	bstra	ct		iii
A	ckno	wledge	ements	iv
Li	st of	Figur	$\mathbf{e}\mathbf{s}$	viii
Li	st of	Table	\mathbf{s}	ix
\mathbf{A}	bbre	viation	ns	х
1	Intr	oduct	ion	1
	1.1	Interc	ountry and international adoptees	. 1
		1.1.1	Levels and trends in intercountry adoption worldwide	. 3
		1.1.2	International adoption in Italy	
	1.2	Role o	of the pediatrician	. 10
		1.2.1	Watch out for the <i>fragile creature</i>	. 14
	1.3	Illness	ses and dysfunctions under exam	. 15
		1.3.1	Infectious diseases	. 16
			1.3.1.1 Tuberculosis	. 16
		1.3.2	Blood count disorders and deficiency states	. 16
			1.3.2.1 Iron-deficient anemia	. 16
			1.3.2.2 Vitamin D deficiency	. 17
		1.3.3	Height-weight disorders	. 17
2	Ma	terials	and Methods	18
	2.1	The p	opulation in exam	. 20
		2.1.1	Inclusion and exclusion criteria	. 23
	2.2	The d	ataset	. 23
	2.3	Datas	et elaboration	24

Contents vi

		2.3.1	VBA ex	pre	ssior	1S .											 				24
		2.3.2	Cut-off	valu	ies												 				25
			2.3.2.1	$\mathrm{H}\epsilon$	eight	t an	d W	Veig	ht								 				25
			2.3.2.2	На	aemo	oglo	bin										 				26
			2.3.2.3	Μ	CV												 				27
			2.3.2.4	Fε	erriti	n .											 				28
			2.3.2.5	Ci	ircul	atin	ıg Iı	con									 				29
			2.3.2.6	Vi	itam	in I)										 				29
		2.3.3	Parasite	es gi	roup	ing											 				30
	2.4	Statist	tical Anal	lyse	s .												 				31
3	Res	ults																			33
	3.1	Descri	ptive ana	alyse	es.												 				33
	3.2		zing the c																		34
	3.3		tical infer																		35
4	Disc	cussion	1																		37
_	4.1		- 1 status o	of in	tern	atio	nall	lv a	dor	oteo	l c	hil	dre	en		_		_		_	37
	4.2		rything w					~	_												38
	1.2	4.2.1	What w																		38
		4.2.2	And wh																		38
	4.3		g for sup																		39
	4.4		tives achi	-			_														39
	4.5		e work .																		39
Α	Dat	aset el	aboratio	on:	VB	SA (exp	res	sio	ns											40
	A.1		n years)				-										 				43
	A.2		aphic are																		
		_	logical va		-	_															45
		A.3.1	Weight a																		45
		A.3.2	Haemog		`	_															46
		A.3.3	MCV.	-																	48
		A.3.4	Circulat																		51
		A.3.5	Ferritin	_																	51
		A.3.6	Vitamin																		52
	A.4		tic Infect:																		53
	4 1. I	A.4.1	Parasite																		53
			Parasite	-																	54
		/) . T . △	-1 $a_1a_2a_3a_4$, 211	フロロコ	115											 	-			• , -+

Con	tents	Vii

Bibliography 56

List of Figures

1.1	Adoptions to US by top countries from 1999 to 2016	7
2.1	Our population's origin distribution by year. Total of children visited via the screening protocol, stratified by geographic area of origin	22
3.1	Boxplot of our population's age distribution (in months) stratified by our four zones and Mantoux test results	35
3.2	Scatter plot of Vitamin D and Haemoglobin values	36

List of Tables

1.1	Countries of destination with the largest number of intercountry adop-	
	tion	4
1.2	Countries of origin with the largest number of intercountry adoption.	5
1.3	Countries with the highest percentual international adoptions	6
1.4	Intercountry adoptions by Italian regions, years 2016 and 2017	9
1.5	American Academy of Pediatrics' recommended screening tests for	
	international adoptees upon U.S. Arrival	14
2.1	Employed haemoglobin cut-off values	26
2.2	Employed MCV cut-off values	
2.3	Employed Vitamin D cut-off values	
3.1	Absolute values and percentages of immunization status of our population, divided by region	34
A.1	Full column-parameter correspondence, including units of measurement or cell type and a short description	43

Abbreviations

GLNBI Gruppo di Lavoro Nazionale per il Bambino Immigrato

HIV Human Immunodeficiency Virus

STI Sexually Transmitted Infection

FASD Feto Alcohol Spectrum Disorders

MCV Mean Corpuscolar Value

VBA Visual Basic for Applications

Chapter 1

Introduction

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

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

1.1 Intercountry and international adoptees

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

requiring medical attention (see [11]). Compared to 19% of the general population, approximately 39% of adopted children require special healthcare attention (as extensively explained in [1]). They are of school age, 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 [1]), 8.868 more in 2012 and 4.714 in 2017 (see [3]). It's estimated that more than 125.000 children have been adopted in the United States alone since 1986 (source can be found in [11]). Further data on annual U.S. international adoptions and their social and financial costs can be found at [4]. More in-depth medical issues will be discussed in Section 1.2.

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

Moreover, as in [2], internationally adopted children may withstand a number of juridical and social impairments even after adoption. No generalization can be made on this matter though, since laws and policies greatly 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 to the emotional and psychological stress of new surroundings, new affections, new habits, and even

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

1.1.1 Levels and trends in intercountry adoption worldwide

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

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

Destination countries are led by the United States with over 127.000 total adoptions in 2001 Even though it accounts for nearly half of all adoptions, only 15% of American families decide to take care of a child coming from outside the US. France and Spain (both with significant annual adoptions, ranging from 4.000 to 5.000 adoptions per year), instead, embrace 80-90% of all adoptions from foreign lands, although they have far less total adoptions per year. Almost all countries adopt primarily from China and Russia, confirming data are shown in 1.2. The median percentage of international adoptions in all examined countries is 64 a remarkable value and effort in helping children from developing countries.

The Italian adoption status will be discussed in 1.1.2.

Rank	Rank Receiving country ¹		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
Media	n	370	64	

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

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

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

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

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

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

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

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

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

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

Table 1.3: Countries with the highest percentual international adoptions.

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

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

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



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

Source: U.S. State Department

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

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

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

1.1.2 International adoption in Italy

According to [7], [8] and [9], in 2014 Italy was the European country with the highest rate of adoptions and the second one worldwide, following the United States. This major role was confirmed in the next two-year period: 2.716 children were adopted from foreign countries in 2016-2017 (see [10]), keeping Italy second worldwide for international custody transfers (see [5] and [6]). As of [2], in 1999 Italy was the fourth country worldwide for international adoptions with 2.177 international adoptions, amounting to 68% of national total. Most of the Italian adoptees are from the Russia Federation (as shown in Table 1.1) and Italy is Bulgaria's favorite country of destination (in Table 1.2).

	Ye	ear 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 [10].

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

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

Most of these children, between 40 and 50%, span between 5 and 9 years of age at their arrival in Italy, and less than 15% are 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 [10]). The children originating from these countries amount to 73% of the total international adoptions.

1.2 Role of the pediatrician

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

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

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

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

Reference [1] states that results of specific diagnostic studies and laboratory tests performed in the country of origin should not be relied on and should be repeated once the child arrives in the country of destination. Paradoxically, review of the child's medical records may raise more questions than provide answers, because of poor translation and use of medical terminology and medications that are unfamiliar to 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 [11], [14], [7], and [8]). In this matter, particular attention should be paid to FASD, as [7] and [8] suggest; according to these studies, more than 17% of all internationally adopted children evidenced special needs, in which FASD is the most common condition observed. Chansoff et al. in [25], in a sample of 547 foster and adopted children reported that 86.5% children with FASD had never been previously diagnosed. Special attention should be paid to children originating from Russia.

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

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

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

Although concern about HIV infection causes considerable anxiety amongst the general population, very few internationally adoptees were found positive to HIV testing (see [11]). Either HIV-infected children do not survive long enough to complete an international adoption procedure or local screening identifies infected children and removes them from consideration for adoption.

Internationally adopted children have often experience pre- and perinatal complications, such as exposure to drugs and alcohol during gestation, the absence of perinatal care, low birth weight, and prematurity (see [24]). Although this is widely known and well documented, several systematic reviews and eminent periodicals focused on infectious disease risk among internationally adopted children, while data regarding prevalence and spectrum of non-infectious conditions, including special needs, FASD and labio-palatal schisis, are poor (see [7] and [8]). At the time of adoption, many children exhibit delays in at least 1 area of development, but most exhibit significant gains within the first 12 months after adoption. Those adopted before 6 months of age usually demonstrate typical development, whereas those adopted at older ages have more variable outcomes (see [1]). 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 the most recent literature reviews concerning international adoptees' health evaluation, vitamin D serum levels are usually left out. This is contradictory with many other papers (see [29], [30], [31], and [32]) that strongly advise towards the relevance of this test for the well being of the child. Internationally adopted children often suffer from vitamin D deficiency or insufficiency, because of the profound change in latitude they experience during the adoption phase, or because of malnutrition combined with lack of solar exposure during pre-adoptive care, usually in orphanages.

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

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

Screening tests

Complete blood cell count

Hemoglobin identification

Blood lead level

Urinalysis

Newborn screening²

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: HBsAgand anti-HBs Ab^3 Neisseria gonorrhoeae and Chlamydia trachomatis testing

Hepatitis C virus serologic testing³ Hepatitis A virus serologic testing

Varicella virus serologic testing

Syphilis serologic testing: Treponemal and

Non-treponemal tests

Human immunodeficiency viruses 1 and 2 $\operatorname{testing}^{3,5}$

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 assav^{3,6}

Chagas disease serology Malaria thick and thin smears Urine for O&P for schistosomiasis⁴

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

1.2.1 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 [12], prior to adoption, or at the time of entry into the family unit, the pediatrician should

²Only for children younger than 12 months of age.

³To be repeated 3-6 months after arrival.

⁴Only if hematuria is present.

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

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

begin a careful medical assessment of the child and should counsel the family appropriately regarding adoption issues. Pediatricians should be alert to the following potential problems:

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

1.3 Illnesses and dysfunctions under exam

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1.3.1 Infectious diseases

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1.3.1.1 Tuberculosis

it can occur.

1.3.2 Blood count disorders and deficiency states

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1.3.2.1 Iron-deficient anemia

it can occur.

1.3.2.2 Vitamin D deficiency

it can occur too.

1.3.3 Height-weight disorders

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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 they have been previously advised by adoption organizations or their trusted pediatrician. 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, etc...) 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 [20], [21], and [22].

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 [13]).

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, Syphilis, HBV, HCV, blood count, erythrocyte sedimentation rate, 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.

The aim of this study was 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 maybe 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 "textitsimplified through knowledge": tests should strictly be ordered only if their outcome changes your subsequent operative choices.

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 2.4.

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 population in exam

285 internationally adopted children were evaluated from January 1st, 2002 to December 31st, 2017; 102 were female (36.17%) and 180 male (63.83%). The 3 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 2 months after their arrival in Italy $(m = 2.23 \text{ and } \sigma = 2.07)$.

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 2.1.1 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
- \bullet 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.

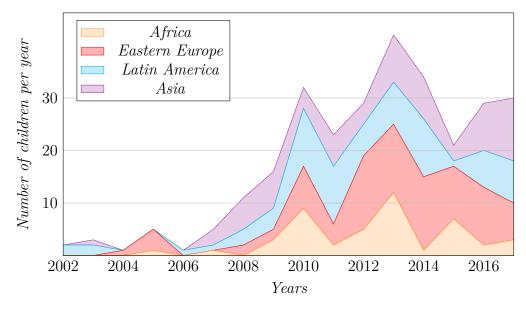


FIGURE 2.1: Our population's origin distribution by year. Total of children visited via the screening protocol, stratified by geographic area of origin.

2.1.1 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 of time, 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 precise 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 considered limited, allowing us to consider the close-to-be entirety of the examined children.

As expressed in Section 2.1, we consider our study group to be highly representative of the population in exam: international adoptees.

2.2 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).

The data was collected on an Excel spreadsheet during the years, normally 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 40, Table A.1 portrays the spreadsheet's full column-parameter correspondence, including units of measurement or cell type and a short description.

2.3 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 33. 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 2.3.1). In Section 2.3.2 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 2.3.3, a particular mention will be made on gastrointestinal parasites.

2.3.1 VBA expressions

In order to allow 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 40.

2.3.2 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 an extensive research of the most recent medical literature. Every parameter will be now discussed on its own in the following sections.

2.3.2.1 Height and Weight

According to [39], [42], and [43] 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 [39], [40], and [41]), 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".

Materials and Methods

26

2.3.2.2 Haemoglobin

Any physician knows that determining whether an haemoglobin value is pathological or not is impossible without any other knowledge of the patient's demographic information, physiological state, usual habits, etc... The major 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 an 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 [36]. 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	≥ 110	100 - 109	70 - 99	≤ 69
Children 5-11 years of age	$\geqslant 115$	110 - 114	80 - 109	≤ 79
Children 12-14 years of age	$\geqslant 120$	110 - 119	80 - 109	≤ 79
Non-pregnant women	$\geqslant 120$	110 - 119	80 - 109	≤ 79
Pregnant women	≥ 110	100 - 109	70 - 99	≤ 69
Men	$\geqslant 130$	110 - 129	80 - 109	≤ 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 [36])

¹All 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
 - Mild²
 - 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 46.

2.3.2.3 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)

Materials and Methods

Therefore we based our cut-off values for MCV on a recent review published on the *International Journal of Laboratory Hematology* (see [37]), 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.

	Fem	ale	Ma	le
Age	Ferritin ³	MCV^4	Ferritin ³	$\mathrm{MCV^4}$
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: Asberg et al. on International Journal of Laboratory Hematology (see [37])

A full technical overview of how this was implemented in the dataset elaboration can be found at Section A.3.3 on page 48.

2.3.2.4 Ferritin

Serum ferritin dosage is a direct marker of the patient's iron storage status. Thus, we recorded its value to further understand the etiologic nature of anemias in our population. 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 51.

³All ferritin values are expressed in ng/ml.

⁴All MCV values are expressed in fl.

2.3.2.5 Circulating Iron

The serum circulating iron value was defined as normal if it belonged to the interval $16-129\mu g/dl$, 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 51.

2.3.2.6 Vitamin D

Vitamin D deficiency and insufficiency are a major health issue in internationally adopted children, as explained in 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 [38]. Moreover, [33], a statistically strong and recent Italian review on a pediatric population, supports this statement, just as the reviews in [34] and [35].

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

Materials and Methods

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	≥ 20	19–10	9-4	≤ 3
nmol/l	$\geqslant 50$	49 - 25	24 - 10	≤ 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 [33])

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 52.

2.3.3 Parasites grouping

Gastrointestinal infestations are a common disease in internationally adopted children, as stated in 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 53.

2.4 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 test 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 study 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*.

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; the full discussion will be tackled in Chapter 4 on page 37.

3.1 Descriptive analyses

As stated in Section 2.1, 285 internationally adopted children were evaluated from January 1st, 2002 to December 31st, 2017; 102 were female (36.17%) and 180 male (63.83%). The 3 missing children are due to sex never being registered in the dataset. Males 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 $(m = 2.23 \text{ and } \sigma = 2.07)$.

The evaluated children born all over the world, 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 2.1), cumulatively,

Results 34

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.

As for immunization status, only 87 (34.25%) showed a completely valid immunization to vaccine-preventable disease. Almost 65% of all children was found to have insufficient antibody levels for at least one of the considered diseases. 3 children were completely exposed. The following Table 3.1 shows the immunization status, considered as complete, incomplete or absent for every considered geographical region. Africa resulted being the region with lowest immunization rate (just over 10%.).

	In			
$Region^1$	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 3.1: Absolute values and percentages of immunization status of our population, divided by region.

3.2 Analyzing the costs

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

Results 35

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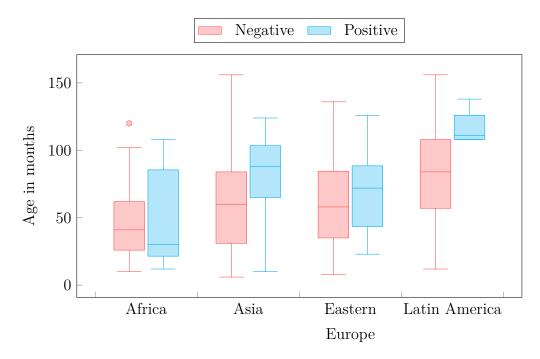


Figure 3.1: Boxplot of our population's age distribution (in months) stratified by our four zones and Mantoux test results.

3.3 Statistical inference of data

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Results 36

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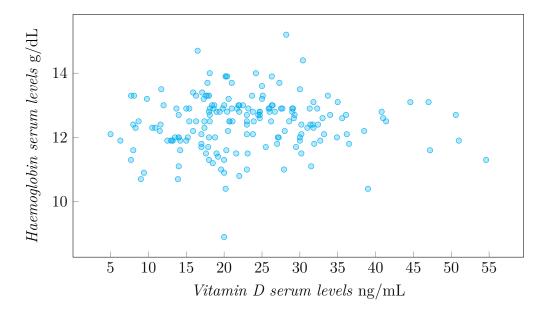


FIGURE 3.2: Scatter plot of Vitamin D and Haemoglobin values

Chapter 4

Discussion

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4.1 Health status of internationally adopted children

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Discussion 38

4.2 Is everything we do worthwile?

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4.2.1 What we believe to be worthwile

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4.2.2 And what may not be

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Appendices 39

4.3 Seeking for support: building correlations

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4.4 Objectives achieved

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4.5 Future work

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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 elaborating data in Excel spreadsheets. Further information can be found throughout this thesis, especially in Section 2.3 on page 24 and cut-off values, parameter by parameter, can be found at Section 2.3.2.

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

Column	Parameter	Units or cell type	Description
\overline{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 infor-
			mation 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	text	E-field was divided in 4 macro-
	origin		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	boolean	Is the child anemic?
	haemoglobin		
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	$\mu \mathrm{g}/\mathrm{dl}$	How much free iron is circulating
			in the child's blood?
Q	Pathological circulat-	boolean	Is the $Q - field$ low or not?
	ing iron		

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

R	Ferritin	ng/ml	Amount of circulating ferritin. This was used to confirm iron-
S	Pathological ferritin	boolean	deficiency anemia. Is the $R - field$ low or not?
T	Feces	text	List of microorganisms found in
-	10000		triple direct microscopical exams
			on three fecal samples. The "neg-
			ative" 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 Enta-
			moeba? This parasite belongs to
			Group 1.
W	Ancylostoma	boolean	Is the child infected with Ancy-
			lostoma? This parasite belongs to
			Group 1.
X	Trichuris	boolean	Is the child infected with
			Trichuris? This parasite be-
17		, ,	longs to Group 1.
Y	Group 2 parasites	boolean	Is the $T-field$ positive for one of
7	Giardia	haalaam	the following parasites? Is the child infected with <i>Giardia</i> ?
Z	Giardia	boolean	This parasite belongs to <i>Group 2</i> .
AA	Strongyloides	boolean	Is the child infected with Strongy-
7171	birongyloides	oootean	loides? This parasite belongs to
			Group 2.
AB	Hymenolepis	boolean	Is the child infected with Hy -
	v 1		menolepis? This parasite belongs
			to Group 2.
AC	Blastocystis	boolean	Is the child infected with Blasto-
			cystis? This parasite belongs to
			Group 2.
AD	Endolimax	boolean	Is the child infected with En -
			dolimax? This parasite belongs to
			Group 2.
AE	Immunization status	text	Complete, incomplete or negative
			immunization statuses on manda-
			tory 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 ROUNDOWN function, in order to avoid overestimating children's age.

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

A.2 Geographic area of origin

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

- Africa
- Asia
- Eastern Europe
- Latin America

A more in-depth overview on how geographic zones where dealt with can be found in the Section 2.1.

```
=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. Cutoff values for these results were established via the most recent literature review, as explained in Section 2.3.2. In the following sections, the code used to establish which of these results where pathological and which were not is displayed and shortly explained.

A.3.1 Weight and height

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

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

A.3.2 Haemoglobin

Hemoglobin required a more complicated and sophisticated expression, in order to be stratified, because hemoglobin pathological cut-offs depend on various factors, as described in Section 2.3.2.2. Moreover mild, moderate and severe anemias had to be differentiated from one another in order to properly evaluate the child's health status. Each one had an arbitrary value of 1 (mild), 2 (moderate) or 3 (severe) associated to it.

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

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

```
2;
3
)
)
)
)
);
```

A.3.3 MCV

Just as described for hemoglobin, MCV required more complicated techniques in order to be stratified, because of its variability (through age, sex, etc...), as described in Section 2.3.2.3. 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 simply comparing the result to the normality interval:

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

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 2.3.2.6.

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

A.4 Parasitic Infections

As explained in Section 2.3.3 on page 30, parasites were subdivided into two groups. In the following sections, it's explained 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 a 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):

This method was used for all the considered pathogens (listed in Section 2.3.3) 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:

The following expression was used for group 2 parasites:

```
AD2
);
1;
0
);
""
```

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