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Acute Respiratory Tract Infections in children at 24 month of age: Cumulative Incidence and Risk factors

Margarida Clara Rodrigues Mota Vieira

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Abbreviations List

ARTI – Acute respiratory tract infections

CI – Confidence Interval

DGS - Health General Directorate

ETS - Environmental Tobacco Smoke

Hib - Haemophilus influenzae type B

LRTI – Lower respiratory tract infections

OM – Otitis Media

OR – Odds Ratio

PCV7 – Heptavalent pneumococcal vaccine

UK – United Kingdom

URTI – Upper respiratory tract infections

USA – United States of America

WHO - World Health Organization

Resumo

Em todo o mundo as Infecções Agudas do Tracto Respiratório (IATR) são consideradas uma das principais causas de doença aguda, responsáveis por uma elevada morbilidade e mortalidade, principalmente nas crianças. Além das causas microbiológicas das IATR, foram identificados factores de risco, como a exposição ao fumo ambiental, tabagismo materno durante a gravidez, frequentar um infantário, baixo peso ao nascer e aleitamento artificial.

O conhecimento da distribuição e dos determinantes de IART é um passo importante para determinar e elaborar estratégias ou políticas de saúde eficazes relativamente à saúde das crianças.

O objectivo do estudo foi calcular a incidência cumulativa e identificar os determinantes das IATR nas crianças com 24 meses de idade de uma coorte de crianças nascidas na área metropolitana do Porto, Portugal - Geração XXI. O presente estudo incluiu os dados de uma sub-amostra de 719 crianças avaliadas aos 24 meses de idade através de questionários aplicados aos pais ou familiares. A informação sobre o *outcome* teve como base os dados colhidos quando as crianças tinham dois anos idade, sendo que os participantes foram questionados se nos 12 meses anteriores, a criança teve alguma otite, bronquiolite, pneumonia ou amigdalite. As variáveis independentes analisadas neste estudo foram: escolaridade da mãe, aleitamento materno, peso da criança ao nascer, idade gestacional, sexo, tabagismo materno durante a gravidez, rendimento do agregado familiar, quem cuida da criança, tabagismo materno, tabagismo paterno e exposição ao fumo passivo.

Foram calculados *odds ratio* (OR) brutos e ajustados, por regressão logística e respectivos intervalos de confiança a 95% para avaliar a magnitude das associações entre as exposições e a ocorrência de IATR.

Com base na informação obtida a partir dos questionários aplicados aos pais verificou-se que, 36,6% das crianças tiveram otite, 17,2% bronquiolite, 1,7% pneumonia e 27,2% tiveram amigdalite nos 12 meses anteriores à aplicação do questionário. A incidência cumulativa de ITR (considerando bronquiolite, pneumonia e amigdalite) foi de 33,4% (IC95% 30-37) e a incidência cumulativa de otite foi de 36,6% (IC95% 33-40). As crianças que frequentavam um infantário tiveram um risco mais elevado de ocorrência de IATR (OR = 2,76 IC 95% 1,90-4,00) e otite (OR = 2,77 IC 95% 1,95-3,93). As mães com níveis de escolaridade mais baixos apresentaram um risco elevado dos seus filhos desenvolverem IATR (OR = 2,16 IC 95% 1,31-3,55) e otite (OR = 2,46 IC 95% 1,52-3,96).

Em conclusão, as IATR apresentaram uma prevalência elevada, especialmente a otite. Os resultados indicam que o facto de a criança frequentar o infantário e o nível de educação da mãe são factores de risco importantes para o desenvolvimento de IATR no segundo ano de vida.

Abstract

Worldwide Acute Respiratory Tract Infection (ARTI) are considered the leading cause of acute illness, responsible for significant morbidity and mortality, particularly in children. Besides ARTI microbiological causes, several risk factors for ARTI have been identified, such as child care attendance, exposure to gestational and environmental smoke, premature birth, low birth weight, formula feeding and agglomeration of people.

A better knowledge of the distribution and determinants of ARTI in our population is important to develop and design effective strategies and health policies concerning the children's health.

The aim of the present study was to determine the cumulative incidence and the factors associated with ARTI and otitis in Portuguese children at 24 months of age, from Porto Portugal, enrolled in the birth cohort *Geração XXI*. A sub-sample of 719 children were evaluated at 24 month by questionnaires applied to parents or relatives.

Outcome information was based on the information when children were two years old, participants were asked if over the past 12 months, the baby had ear infections, bronchiolitis, pneumonia or tonsillitis. The independent variables of interest used in this analysis were: mother's education, breastfeeding, birth weight, gestational age, sex, gestational smoke, family income, day care, maternal smoking, paternal smoking and passive smoke. Crude and adjusted odds ratio (OR), and their respective 95% confidence intervals were calculated by unconditional logistic regression, to measure the magnitude of the associations between factors, ARTI and otitis.

Based on information reported by parents or relatives, 36.6% of children had otitis, 17.2% had bronchiolitis, 1.7% had pneumonia and 27.2% had tonsillitis, in the previous 12 months. The overall cumulative incidence of ARTI (considering bronchiolitis, pneumonia and tonsillitis) was 33.4% (CI 95% 30-37) and the cumulative incidence of

otitis was 36.6% (CI 95% 33-40). Children attending a day care centre had a significantly higher risk of ARTI (OR=2.76 CI 95% 1.90 – 4.00) and otitis (OR=2.77 CI 95% 1.95 – 3.93). Mothers classified into lower level education classes presented a higher risk of their children to develop ARTI (OR=2.16 CI 95% 1.31 – 3.55) and otitis (OR=2.46 CI 95% 1.52 – 3.96). No associations were found between the other studied variables and the occurrence of ARTI.

In conclusion, ARTI are highly prevalent, especially OM. The results support that attending a day care center and level of mothers' education are important risk factors for developing ARTI.

1. INTRODUCTION

World Health Organization (WHO) recognized infectious diseases as a global threat to public health, with a huge impact on people's life[1]. Acute respiratory tract infections (ARTI) are considered one of the most important diseases, not only by the number of people affected but also, by its severity and spreading capability[16].

In 2004, the WHO Global Burden of Diseases update estimated that ARTI were responsible for 4.2 million deaths in all ages, 1.8 million among children aged from one to 59 months, and the percentage of deaths attributable to ARTI, in children younger than five years, was 17% to 23%[2,3] .

In order to define policies, it is of most importance to study and understand the determinants of ARTI. The globalization and the mobility around the world, increased the possibility of infections spreading, especially ARTI, as they can easily be transmitted from one person to another by a simple exchange of respiratory droplets. For this reason, knowledge has become the key element for implementing effective measures to reduce this possibility. Knowing and intervening directly in the risk factors that trigger ARTI helps to reduce its prevalence.

WHO recommends that, in developed countries, evidence about ARTI should be systematically evaluated in order to promote effective methods of prevention, treatment and develop guidelines for antibiotic prescribing[10,16].

Acute Respiratory Infections in children

The development of medical care and the improvement of life conditions, in the last decades, particularly in developed countries, were the main factors leading to better children´s health indicators. Nutrition, basic sanitation, potable water, vaccination,

antibiotherapy, social and health policies, have contributed significantly to better health, reducing mortality and increasing the population´s quality of life[4].

ARTI are considered by the WHO as a forgotten pandemic[16], worldwide considered as the leading cause of acute illness particularly in children, responsible for significant morbidity and mortality[5,6,7,8,9]. ARTI are the main cause of death in children under five years old in developing countries, most of these caused by pneumonia[10,16,]. ARTI are classified into upper and lower respiratory tract infections (URTI, LRTI), depending on the main organs affected. URTI are defined as acute infections that affect the airway above epiglottis including the involvement of nose, sinuses, middle ear, larynx and pharynx[11]. LRTI are defined as acute infections that affect the airway below the epiglottis involving trachea, bronchi and lungs. LRTI can also be combined with any URTI[13].

The proportion of mild to severe disease varies between high and low income countries[12]. The severity of lower respiratory tract infections in children younger than five years is worse in developing countries, resulting in a higher case-fatality rate[12]. The costs of ARTI are enormous, as they lead children and their family to health care facilities with a remarkable number of doctor´s visits, hospital admissions and health care costs[6,13,14.] In the United States of America (USA), URTI are the most common illness, responsible for absence from work or school[15]. In developed countries, ARTI are the leading cause of morbidity, accounting for 20% of medical consultations, 30% of labor absenteeism and 75% of all drug prescriptions[16,10]. Many of these prescriptions are unnecessary because drug therapy has little or none effect on viral URTI[10].

Respiratory diseases cover a wide spectrum of children´s pathological events, with different etiologies and severity[14]. ARTI can occur in any part of the respiratory system from the middle ear to nose and lungs[17].

In developing countries the severity of infections, such as LRTI is more significant, resulting in a higher case fatality rate. The severity of LRTI is higher when patients are children, elderly or immune-compromised individuals[11].

URTI are the most common infectious diseases, as they are contagious and can be spread from one person to another by inhaling respiratory droplets from coughing and sneezing, oral contact or indirectly by hands or objects recently in contact with respiratory discharges from an infected individual[18,19]. A substantial part of ARTI are associated with viruses[12,18], like *rhinovirus*, respiratory *syncytial* virus, *parainfluenza* and *influenza* viruses, human *metapneumovirus*, *adenovirus* and *coronavirus*[6]. Usually these infections are self limited[11] and complications are more important than the infection itself[12]. Nevertheless bacterial agents can be found in some of children's ARTI[20]. Acute viral infections predispose children to bacterial infections and aspiration of infected secretions can result in a LRTI[12].

The most common LRTI in children are pneumonia and bronchiolitis[12]. Bronchiolitis occurs predominantly in the first year of life and its frequency decreases in the second and third years[12]. Both bacteria and virus can cause pneumonia[12]. Bacterial pneumonia is often caused by *Streptococcus pneumonia* or *Haemophilus influenza*[12]. Pneumonia kills more children than any other illness in the world[21], the majority of deaths occurring in Africa and South-East Asia[22]. According to WHO, in the European Region (2008), pneumonia caused 11% of total deaths in children under five years old.

Tonsillopharyngite is caused by viruses in more than 70% of cases in young children[12]. *Streptococcal* infection is rare in children under five and more common in older children[12].

ARTI in children are associated with otitis media (OM) and some studies indicate that OM account for most bacterial respiratory infections in children both in developed and developing countries[7,23,24]. OM represents one of the most common childhood

infections[25,26]. Ear infection occurs with up to 30 percent of total URTI[12]. OM is one of the leading causes of children medical visits and the most frequent reason for children to receive antibiotics or undergo for surgery[27].

Studies have shown that peak rates of ARTI occur in the first two years of life (approximately five episodes per year) and decrease thereafter[28]. A 900 children European multicentre cohort study, found that French and Italian children averaged 4.26 episodes of URTI each year[29].

Viral respiratory infections are the main pediatric cause of infant's hospitalization worldwide[30]. Most studies focus on prevalence and incidence of hospitalized children[31,32]. Portuguese data on ARTI is scarce, the information available includes the number of hospitalizations by diseases or diagnostic group and age.

In Portugal, between 2004 and 2005, the second highest number of hospitalizations of children younger than one year was caused by respiratory diseases being only preceded by a diagnostic group "other categories" which included birth delivery hospitalizations[33]. Data showed that respiratory diseases were the first cause for hospitalization in children from one to fifty years[33]. Concerning children of one to fifty years of age, the second highest diagnostic group in number of hospitalizations was tonsillectomy and/or adenoidectomy, probably due to recurrent infections[33].

Regarding the global available data, a constant effort should be maintained for the next generations, in order to decrease the number of hospitalizations and deaths associated with ARTI. WHO recommends that routine immunization programmes in all countries should include four vaccines that prevent pneumonia – measles, pertussis, haemophilus and pneumococcal conjugate[21]. *Streptococcus pneumoniae* is the most common cause of severe pneumonia among children in the developing world, vaccines to protect against this infection are available for adults and children[17].

Vaccination, mainly in developed countries, is one of the strategies that have been implemented and must be reinforced throughout the world to prevent ARTI. Several vaccines against ARTI are in use or being implemented, such as the vaccine against *haemophilus influenza type b* (Hib) introduced in North America and Western Europe in the early 1990´s[12]. After the advent of these vaccines incidence decreased dramatically in developed countries.

In Portugal, vaccines are given free of charge in health facilities of the National Health Service, following the schedule and technical guidelines of the Portuguese National Vaccination Programme[34]. Portuguese infants are routinely immunized against several diseases, such as, diphtheria, tetanus, pertussis, polio, haemophilus influenza type b, hepatitis B and neisseria meningitidis group C, with high infant immunization coverage. Vaccine coverage in the Northern Health Region of Portugal is high[34,35]. Since the birth cohort of the year 2000, in the Northern Health Region of Portugal, vaccines from the national vaccination programme presented a coverage rate higher than 95%, evaluated at two years old[35]. In Portugal pneumococcal vaccines were not included in the national programme of vaccination, but in the year 2010 the General Health Directorate (DGS) introduced this vaccine for children and teenagers belonging to risk groups[36]. This vaccine was already available in the market for some years, and children have been vaccinated according to medical advice. In the Northern Health Region of Portugal vaccinal coverage for pneumococcal vaccine of children born in the year of 2004 was around 43.1%[37].

Worldwide interventions to control ARTI can be divided into four basic categories: immunization, early diagnosis and treatment of disease, improvements in nutrition and safer environments[12]. In order to prevent the spread of an infection, hand washing is the mainstay for reducing the risk of contracting ARTI[18,26]. Another important measure is that people with ARTI should reduce contact with others, in order to avoid the spread

of infection[18]. Preventive measures such as vaccination against measles, pertussis and Haemophilus influenzae type b, and improved nutrition can help decrease the incidence and lessen the severity of respiratory infections[22].

Determinants of ARTI

Besides ARTI microbiological causes[14], several risk factors for ARTI have been identified, such as child care attendance[38,39], having older siblings, exposure to gestational and environmental smoke, young motherhood, low socioeconomic status[40], male gender, premature birth, low birth weight, born during winter, formula feeding[13], agglomeration of people and climate changes[41]. Breastfeeding has been described as a protective factor against ARTI[27].

Demographic, Social and Economic determinants

There is overwhelming evidence that health status differ according to sex[42]. Newborn girls are more likely to survive to their first birthday than newborn boys[43]. This advantage continues throughout life: women tend to have lower rates of mortality at all ages, probably due to a combination of genetic and behavioral factors.

A study published in 2000 stated that boys during the first year of life had 1.5–2.0 times the incidence of LRTI illness in comparison with girls[44].

A consistent association between socio-economic position and health status has been also described[45]. Socioeconomic indicators, including education and income, are the strongest predictors of health[4]. Studies using any reasonable indicator of socioeconomic status have shown that poor individuals are those who are less educated[46]. Income is a measure of economic position. Many studies have examined

the relationship between income, health in older age and differences in mortality between populations[47,48]. Household income was inversely associated with self-reported poor health after adjusting for other socio-economic factors[47,48]. Higher family income leads to higher education and consequently to better information about health and health management[47].

Studies showed education to be a potentially important determinant of health status in later life, probably in the establishment of subsequent social and economic trajectories, but also potentially through the promotion of healthy behaviours and by increasing options when dealing with illness and stress[47].

Unmeasured factors such as social status are often evaluated by the income of the individual or family[48]. The improved educational and socioeconomic status of the individual and his family reduces several risk factors for ARTI such as: agglomeration of people, promotes better access to health care, reduces risks of low birth weight and malnutrition[28].

Peri-natal outcomes

Pre and postnatal psychosocial factors influences health throughout life[47].

Both preterm and intrauterine growth-restricted babies have depressed immune function, and epidemiologic studies have demonstrated some of the possible clinical implications of this with increased mortality from infections in low birth weight children[49].

A USA cohort study of 50 000 children found that moderate low birth weight (1500g - 2499g) when compared birth weights at or above 2500g had an increased risk of infections diseases mortality of 150%[49]. A depressed immune status is a result of the association between low birth weight and infectious diseases[49].

Child care attendance

In developed countries women are fully integrated in the labor market resulting in lifestyle changes. Women no longer stay at home taking care of their house and children. Nowadays, children are placed in day care centers while their parents are at work. An important part of their day is spent with other children, usually in closed spaces. The use of day care centers is very common in developed countries, contributing to the complexity of the epidemiology of respiratory diseases and may also help to understand the paradox observed with the simultaneous growth of socioeconomic level of population and childhood respiratory diseases[14].

Evidence shows that attendance at day care centers during the first years of life contributes as an important factor for the presence of ARTI[50,93]. It has been suggested that the increased number of respiratory infections is proportional to the number of contacts between children in day care centers, due to increased exposure to respiratory pathogens[51].

The relation of child care attendance and respiratory infections is stronger in those who enter day care centers at early age [50]. A study conducted in Norway, into 2000, found that attendance at day care centers increased the risk of URTI in children aged four to five years[51].

In 2005, the proportion of children younger than three years attending day care centers throughout Europe was 25% and 84% for children three years old to compulsory school age[52].

Tobacco Exposure

Since the Second World War the consumption of tobacco became widespread, initially consumed by men, followed by women[53]. Tobacco was consumed at home, at work and at school throughout all daily activities[54]. No special attention was given to prevent smoke from reaching young children, pregnant women or non smoking individuals. Smokers affected not only their own health but the health of those around them.

Exposure to cigarette smoking, both in uterus and by passive exposure to environmental tobacco smoke in infancy, has been linked to numerous adverse health outcomes in young children[55,56,57].

According to WHO, 700 million children around the world were exposed to second hand smoke in 1999 which caused significant morbidity and mortality[58]. Children exposure to environmental tobacco increases the incidence of middle ear disease, bronchitis, bronchiolitis, pneumonia, a decrease in pulmonary function and it is also associated with adenoid hypertrophy, tonsillitis, sore throats[59], sudden infant death syndrome[60] and increased number of hospitalizations[58]. It has been described that the incidence of tonsillectomy was double for children who lived in households with smokers[59].

A woman who smokes during pregnancy not only risks her own health but also changes the conditions under which her baby develops, leading to a potential retarded foetal growth[58]. The fetus exposure to prenatal maternal tobacco has an increased risk of low birth weight and higher risk of respiratory disease[59]. A set of systematic reviews concerning the relationship between second-hand exposure to tobacco smoke and respiratory health in children showed evidence of a strong causal relation[61]. There is evidence to infer a relation between a smoking mother and an increased risk for children LRTI illnesses[58].

A study in the USA found a decline in smoking during pregnancy from 1990 to 2003, decreasing from 18.4% to 11%[62]. In another study in USA, the prevalence of smoking during pregnancy declined from 15.2% in 2000 to 13.8% in 2005, and the prevalence of smoking after delivery declined from 18.1% in 2000 to 16.4% in 2005[63].

One of the objectives of the Healthy People 2010 (USA Department of Health and Human Services) was to reduce the prevalence of prenatal smoking to 1%[63].

The results of the Fourth Portuguese National Health Survey (2005/2006) confirmed the relatively low prevalence rate of smoking in Portugal, fact that was already stated out in the former Eurobarometer, that 27.0% of Portuguese population smoked in 2005, in comparison to 29.0% in 2002[64]. In Europe only Slovenia had lower prevalence rates in the same kind of surveys[65]. In the Fourth Portuguese National Health Survey there were more regular male smokers than female. The prevalence of smoking women was 11.2% in 2005/2006[64] and the prevalence of women who smoked in the age group 25 to 44 years was around 20%[66]. A cohort study conducted in Portugal (2003) found a prevalence of smoking before pregnancy of 29.9% and a prevalence of pregnant women smoking of 19.4%[67].

Breastfeeding

Another important determinant of children's health is breastfeeding. While many of the other determinants are studied because of their negative impact on health, breastfeeding is known by its protective effect.

The WHO recommends that all infants should be exclusively breastfed for the first six months of life and continue up to 24 month while complementing with nutritionally appropriate foods [68,69,70,71].

Breast milk is the natural nutrition for all infants and recognized as the preferred one by American Academy of Pediatrics (AAP) [72,73]. Human milk is uniquely superior for infant feeding since it is species-specific[74].

The natural development of children´s immunological system made children less susceptible to agents that can lead to illness. This susceptibility is higher in small children, particularly those younger than two years old, because of their immature immunological functions[75]. When they grow older, the incidence of these infections decreases, probably as a result of a more mature immune system[76].

The epidemiologic evidence reveals that breastfed children are more resistant to infectious diseases and have stronger immune systems[72]. In addition to its nutritional superiority, breastfeeding has been associated with a reduction in the incidence and impact of childhood infections, including respiratory tract infections, otitis media, atopic dermatitis, gastroenteritis, type two diabetes, sudden infant death syndrome, and obesity [2,68, 69,72, 77-82].

The explanation for this enhanced resistance to disease can be found in the biology of human milk[72]. When a lactating mother is exposed to an infectious agent, her mature immune system begins to produce secretory immunoglobulin A [S-IgA], a compound that is the primary disease fighter in the human immune system[72]. Immune factors such as secretory IgA and lactoferrin are primary mediators in infection prevention[83]. This substance is secreted into mother breast milk and consumed by her nursing infant[72]. Breastfeeding provides breastfed children with immunological factors[84] that they are unable to produce[70]. Infants who are breastfed develop advantages that enhance their health throughout their lives[72].

A study conducted in a Mediterranean birth cohort found that the risk of LRTI was lower in infants who were breastfed for more than 12 weeks[85]. A cohort study, published June 2010, found that exclusive breastfeeding until the age of four months

and partially thereafter was associated with a significant reduction of respiratory morbidity rates in infants until the age of 12 months, but they recommended that the effects of prolonged and exclusive breastfeeding on infectious diseases at older ages in industrialized countries should be studied[86].

The present study is an approach for the understanding of which factors are involved in the development of respiratory tract infections diseases among Portuguese children of 24 months of age, enrolled in a birth cohort in the North of Portugal - *Geração XXI.* It is also aims to understand if the exposure to variables that took place in a distant past, such as gestational weight, breastfeeding and tobacco exposure during pregnancy, or if the effect is from more recent exposures.

Most of the mentioned studies that evaluated the risk factors for ARTI, namely gestational tobacco, breastfeeding, birth weight, gestational age, tobacco exposure, were performed in North American or North European populations and considering the first year of life. In southern European populations, particularly in Portugal the information is scarce or inexistent.

A better knowledge of these factors is important to determine and design effective strategies and health policies concerning the health of children.

1.2 Objective

The aim of the present study was to determine the cumulative incidence and the factors associated with respiratory tract infections in Portuguese children at 24 months of age, from Porto Portugal, enrolled in a birth cohort.

2. PARTICIPANTS AND METHODS

2.1 Participants

The present study included data from *Geração XXI* birth cohort coordinated by the Hygiene and Epidemiology Department of the University of Porto Medical School and Institute of Public Health, University of Porto.

The major objective of the project *Geração XXI* cohort aims to characterize the prenatal development and postnatal, identifying modifiable determinants of this development in order to better understand the health status during childhood and later in adolescence and adulthood.

Participants were pregnant women resident in the metropolitan area of Porto who delivered a live born baby between 1 May 2005 and 31 August 2006 at the maternity clinics of the five public hospitals (*Centro Hospitalar de Vila Nova de Gaia, Hospital Pedro Hispano, Hospital Geral Santo António, Hospital São João* and *Maternidade Júlio Dinis*).

These hospitals are responsible for 91.6% of the total deliveries in the catchment population of the metropolitan area of Porto[87], with the remaining occurring in private hospitals/clinics.

A total of 8654 babies were enrolled into *Geração XXI* cohort. From the total participants a sub-sample of 719 were evaluated at 24 month. The sub-sample was selected by contacting consequently parents or relatives when babies completed 24 months.

The characteristics of individuals gathered in the study (n=719) and the remaining individuals who participated in the *Geração XXI* (n=7561) were compared in Table 1.

Mothers of participating children were significantly older and more educated when compared with non participating mothers at 24 months. No statistical differences were observed for: birth weight, gestational age, sex of child and gestational smoke between the two groups of participants.

In the 719 children evaluated, 51.5% were boys, 12.1% were low birth weight and 21.0% were born with less than 38 weeks of gestation. Regarding mothers education, 30.1% had completed 10 to 12 years of education and 18.0% had less than 6 years of completed education. Twenty per cent of mothers smoked during pregnancy.

Table 1 - Baseline characteristics of participants and those non participants at 24 months

	Non Participants at 24 months		Participants at 24 months		
	n = 7561		n = 719		p
	n	%	n	%	
Age Mother (years)					
≤ 20	620	8.2	22	3.1	
21- 30	3843	50.0	400	55.7	<0.001
31-40	2978	39.4	282	39.3	
>40	120	1.6	14	1.9	
Mothers Education (years)					
0-6	1802	23.9	128	18.0	
7-9	1942	25.7	169	23.7	<0.001
10-12	1957	26.5	214	30.1	
≥13	1801	23.9	201	28.2	
Birth weight					
<2500gr	836	11.0	87	12.1	p=0.389
≥2500gr	6735	89.0	632	87.9	
Gestacional Age (weeks)					
≤37	1573	20.8	151	21.0	p=0.887
>37	5998	79.2	568	79.0	
Sex of child					
Male	3798	51.2	359	51.5	p=0.874
Female	3621	48.8	338	48.5	
Gestational Smoke					
No	5732	77.3	565	80.0	p=0.102
Yes	1694	22.7	141	20.0	

Table 2 shows the distribution of other social, clinical and behavioural characteristics of participants.

The questionnaire applied at 24 months was answered mainly by children's parents 93.0%, and in 7.0% of cases was answered by Grandparents. Sixty six percent of participants referred a family monthly income of less than 1500 Euros. Most of the children (56.9%) were taken care by a family member, 32.7% were attending a day care center and 10.4% by a babysitter. Seventy eight percent of children have done pneumococcal vaccination.

Table 2 also shows the distribution of behavioural characteristics, prevalence of parental smoking and prevalence of breastfeeding.

Regarding tobacco consumption, 38.8% of mothers at baseline were currently smokers or ever smokers. At 24 months of age, 21.7% of mothers were smokers and 37.4% of fathers were smokers.

Concerning breastfeeding, 93.5% of mothers have ever breastfed their son. The proportion of mothers who stopped breastfeeding their children before 4 months of age was 41.4% and 28.0% of mothers stopped breastfeeding their children after 6 months of age.

Table 2 – Distribution of other social, clinical and behavioral characteristics of participants.

	n	%
Who answer the questionnaire		
Mother	442	61.6
Father	225	31.4
Grandparents	50	7.0
Family Income		
0 – 1000 €	231	37.0
1001 – 1500 €	181	29.0
1501 – 2000 €	105	16.8
≥ 2001 €	107	17.1
Day Care		
Family	406	56.9
Babysitter	74	10.4
Day Care Center	233	32.7
Pneumococcal vaccine		
Yes	564	78.4
No	155	21.6
Mother Smoke or ever Smoke		
Never	433	60.2
Yes	279	38.8
Maternal Smoking		
No	561	78.0
Yes	156	21.7
Not living with mother	2	0.3
Paternal Smoking		
No	407	56.6
Yes	269	37.4
Not living with father	42	5.8
Ever Breastfed the child		
Never	47	6.5
Yes	672	93.5
Breastfeeding		
No breastfeeding	47	6.5
Until 4 month	298	41.4
4 – 6 months	122	17.0
>6 month	201	28.0

2.2 Methods

At baseline, all the information was collected by trained interviewers using a structured questionnaire. Each participant was inquired about socio-demographic factors, family, lifestyle and health, use of medical care, birth weight, self-reported health status, health risk behaviours including smoking and smoking status of the mother at pregnancy.

The questionnaire applied to parents or other relative of children at two years of age and was divided in nine parts, with both open and closed questions. The questions were related to the following variables: food, hygiene care, sleeping habits, sun protection, surrounding environmental, health, physical exam, breastfeeding, who takes care of child, paternal smoking, maternal smoking and infections in the last twelve months. Data was also gathered from the baseline, mother's questionnaire about maternal smoking during pregnancy, mother's education and family income. Data about sex, weight at birth and gestational age were extracted from the baby's questionnaire at birth.

Data collection at two years old was done by interviewers conducted by face to face interviews.

All procedures involved in the recruitment and follow-up of participants in this cohort (questionnaires, anthropometry in adults and newborns) were tested and professionals have been trained, initially under experimental conditions and subsequently in the real world with the aid of health professionals from different specialties. Questionnaire answers were based on parental or other family report.

The independent variables of interest used in this analysis were: mother's education, breastfeeding, birth weight, gestational age, sex, gestational smoke, family income, day care, maternal smoking, paternal smoking and passive smoke.

Education

Educational level of the mother was recorded as complete years of education and was subsequently classified in four categories of education: less than six years, seven to nine years, ten to twelve years and more than twelve years.

Maternal Tobacco Consumption

Prenatal maternal smoking was assessed in the first questionnaire by asking the mother whether she had smoked during the pregnancy or not. The questionnaire included detailed questions regarding maternal tobacco consumption during pregnancy. Women were asked if they smoked or have ever smoked regularly? If they answered positively, how many cigarettes did they smoked daily in the 1st, 2nd and 3rd trimester? Women were considered smokers during pregnancy if they smoked during any trimester of pregnancy.

Maternal smoking at two years of child life was quantified as if mother smoked. Smokers were considered all those mothers who at the time of the questionnaire reported smoking.

Tobacco maternal consumption was classified into four categories: never, pre-natal only, post-natal only and pre and post-natal.

Paternal Smoking

Paternal smoking at two years of child life was quantified as if father smoked. Smokers were considered all those fathers who at the time of the questionnaire reported smoking.

Passive Smoke

Participants were asked whether they smoked in the presence of children.

Questionnaire asked respondents to quantify how long a day was smoke in contact with their child.

Breastfeeding

Participants were asked if the child was ever breastfed, and the age when the child stopped being breastfed.

The number of months that the child was breastfed was grouped for analysis into four categories: no breastfeeding, until four months, between four and six months and more than six months.

Day Care Attendance

Day care was grouped into three categories: if the child was taken care by any familiar, by a babysitter or was attending a day care center.

Birth weight

Birth weight was collected at birth, and it was used as a categorical variable in the analyses: <2500g (low birth weight) and ≥2500g.

Gestational age

Gestational age was defined into two categories: under or equal to 37 weeks and more than 37 weeks.

Monthly Family Income

Income was classified in to four categories: less than 1000€, between 1001-1500, between 1501 - 2000 and more the 2000€.

Main Outcome Measures

Information on ARTI was based on self-reported information by parents or other relatives about if, in the previous 12 months, children have had one of the following conditions: ear infections, bronchiolitis, pneumonia or tonsillitis.

In the present study two separated outcomes were considered:

- Acute Respiratory Tract Infection was defined if the child had at least one episode of bronchiolitis, pneumonia or tonsillitis in the previous 12 months.
- Otitis was defined if the child had at least one episode of otitis in the previous 12 months.

Ethics

Ethical approval for the study was obtained from relevant institutional ethics committees. In cohort *Geração XXI*, all participants provided written informed consent.

2.3 Statistical analysis

The two-independent samples *t*-test was used to compare mean differences in mother's age between participants and non-participants. The Shapiro-Wilk test was used to assess the assumption of normality. The chi-square test was used to compare proportions.

Crude and adjusted odds ratio (OR), were calculated by unconditional logistic regression, and their respective 95 % confidence intervals were used to measure the magnitude of the associations between factors, ARTI and Otitis. All variables that showed crude OR with a p-value lower than 0.10 were included in the final models.

Data analyses were performed using SPSS version 17.0.

3. RESULTS

Table 3 shows the cumulative incidence of ARTI. Based on information reported by parents or other relatives, 36.6% of children had otitis, 17.2% had bronchiolitis, 1.7% had pneumonia and 27.2% had tonsillitis, in the previous 12 months.

The overall cumulative incidence of ARTI (considering bronchiolitis, pneumonia and tonsillitis) was 33.4% and the cumulative incidence of otitis was 36.6%.

Table 3 – Cumulative Incidence and confidence interval (CI 95%) of acute respiratory tract infections in a year

	Yes		CI95%
	n	%	
Otitis	262	36.6	(33 – 40)
Bronchiolitis	123	17.2	(14 – 20)
Pneumonia	12	1.7	(1 – 3)
Tonsillitis	153	27.2	(24 – 31)
Acute Respiratory tract infection*	239	33.4	(30– 37)

*In this study was defined at least one episode of bronchiolitis, pneumonia or tonsillitis in the last 12 months.

Table 4 and Table 5 show the crude and adjusted OR, for socio-demographic, peri-natal and health behaviours associated ARTI.

In crude analysis and after adjustment for confounders, the level of education was associated with ARTI. Mothers classified into lower level education classes presented a higher risk of their children to develop ARTI, when compared with mothers with 13 or more years of education.

Children attending a day care center had a significantly higher risk of ARTI (OR=2.76 CI 95% 1.90 – 4.00) in relation to children who were taken care by their relatives.

No significant associations were found between factors such as mother's age, breastfeeding, birth weight, gestational age, sex of child, family income, pneumococcal vaccination and ARTI.

Table 4 – Distribution of acute respiratory tract infection according to socio-demographic, peri-natal and behavioural characteristics and respective crude and adjusted odds ratio

Determinants	Acute respiratory tract infection n	%	p	Crude OR (CI 95%)		Adjusted OR (CI 95%) [1]
Age Mother (years)						
≤ 20	7	31.8		1		1
21- 30	133	33.4	0.996	1.08	(0.43 – 2.70)	1.49 (0.48 – 4.59)
31-40	94	33.5		1.08	(0.43 – 2.73)	1.43 (0.46 – 4.45)
>40	5	35.7		1.19	(0.29 – 4.90)	1.01 (0.17 – 5.84)
Mothers Education (years)						1
0-6	42	33.1		1.52	(0.93 – 2.49)	1.68 (0.97 – 2.88)
7-9	67	39.6	0.008	2.02	(1.30 – 3.16)	2.16 (1.31 – 3.55)
10-12	80	37.6		1.85	(1.21 – 2.83)	1.92 (1.20 – 3.05)
≥13	49	24.5		1		1
Family Income						
0 – 1000 €	78	33.9		1		1
1001 – 1500 €	69	38.1	0.324	1.20	(0.80 – 1.80)	1.28 (0.80 – 2.04)
1501 – 2000 €	35	33.3		0.97	(0.60 – 1.59)	1.30 (0.72 – 2.35)
≥2001 €	29	27.4		0.73	(0.44 – 1.22)	1.09 (0.56 – 2.10)
Sex of child						
Male	118	33.1	0.664	1		1
Female	117	34.6		1.70	(0.78 – 1.47)	1.08 (0.76 – 1.52)
Birth weight						
<2500gr	26	29.9	0.461	1		1
≥2500gr	213	33.9		1.20	(0.74 – 1.96)	1.12 (0.67 – 1.88)
Gestational Age (weeks)						
≤37	46	30.5	0,393	1		1
>37	193	34.2		1.18	(0.80 – 1.75)	1.03 (0.67 – 1.58)
Breastfeeding						
No Breastfeeding	15	31.9		1.00	(0.51 – 1.98)	1.03 (0.49 – 2.15)
until 4 Month	109	36.8	0.534	1.25	(0.85 – 1.82)	1.07 (0.70 – 1.65)
4 - 6 Month	37	30.6		0.94	(0.58 – 1.54)	0.84 (0.49 – 1.43)
>6 Month	64	31.8		1		1
Day care						
Family	107	26.5		1		1
Babysitter	20	27.4	<0.001	1.05	(0.60 – 1.83)	1.29 (0.70 – 2.36)
Day care center	111	47.8		2.55	(1.81 – 3.58)	2.76 (1.90 – 4.00)
Pneumococcal vaccine						
Yes	181	32.2	0.203	0.79	(0.54 – 1.14)	1.02 (0.65 – 1.60)
No	58	37.7		1		1

1 – Adjusted for: mother's education, day care, paternal smoking and maternal tobacco consumption.

Table 5 shows the crude OR, adjusted OR for tobacco exposure on ARTI occurrence.

Children exposed to tobacco smoke during pregnancy and after birth presented in crude analysis a significantly higher risk of ARTI, when compared with those not

exposed (OR = 1.86 95% CI 1.21 – 2.84). However, after adjustment for confounders the positive association did not remain significant.

No significant association was found for paternal smoking but regarding the exposure to passive smoking from fathers, children of smoking fathers that referred never have smoked near their children, presented a higher risk of ARTI (OR=1.81 CI 95% 1.12 – 2.93) than children of non smoking fathers.

Children of smoking mothers that have never smoked near their children, presented higher risk of ARTI in crude analyses (OR=1.88 CI 95% 1.15 – 3.07), but this association did not remained significant after adjustment (OR=1.12 CI 95% 0.61 – 2.08).

Table 5 – Distribution of respiratory tract infections according to tobacco exposure and respective crude and adjusted odds ratio

Determinants	Respiratory tract infection			Crude OR (CI 95%)		Adjusted OR (CI 95%) [1]
	n	%	p			
Maternal Tobacco Consumption						
Never	160	30.8		1		1
Pre-natal only	12	35.3	0.044	1.22	(0.59 – 0.53)	1.34 (0.61 – 2.92)
Post-natal only	14	33.3		1.12	(0.58 – 2.19)	0.71 (0.32 – 1.58)
Pre and Post-natal	48	45.3		1.86	(1.21 – 2.84)	1.45 (0.88 – 2.38)
Paternal Smoking						
No	121	30.0	0.079	1		1
Yes	98	36.4		1.34	(0.97 – 1.86)	1.13 (0.78 – 1.65)
Passive Maternal Smoking						
Non Smoker	164	31.1		1		1
Never smoked near the child	34	45.9	0.027	1.88	(1.15 – 3.07)	1.12 (0.61 – 2.08)
Smoked near the child	18	39.1		1.42	(0.77 – 2.64)	1.60 (0.73 – 3.58)
Passive Paternal Smoking						
Non Smoker	121	30.0		1		1
Never smoked near the child	53	44.5	0.012	1.88	(1.24 – 2.86)	1.81 (1.12 – 2.93)
Smoked near the child	27	32.1		1.12	(0.67 – 1.84)	0.78 (0.42 – 1.44)

1 – Adjusted for: mother's education, day care, passive paternal and maternal smoking.

Table 6 shows the crude and adjusted OR, for socio-demographic, peri-natal and health behaviours associated with otitis.

In crude analysis and after adjustment for confounders the level of education was associated with otitis. Mothers classified into lower education classes presented higher risk of their children to have otitis when compared with mothers with 13 years or more of education.

Children attending a day care center had a significantly higher risk of otitis (OR=2.77 CI 95% 1.95 – 3.93) in relation to children who were taken care by their relatives.

Age of the mother presented in crude analysis a significant association, older mothers have a lower risk of their children to develop otitis. However, after adjustment for confounders the positive association did not remain significant.

No significant associations were found between factors such as breastfeeding, birth weight, gestational age, sex of child, family income, pneumococcal vaccination and otitis.

Table 7 shows the crude and adjusted OR for tobacco exposure determinants associated with otitis.

No significant associations were found between the following factors: maternal tobacco consumption, paternal smoking, passive maternal smoking, passive paternal smoking and otitis.

Comparing the two respiratory outcomes ARTI and otitis, the two common variables that explains the risk of infection in the two analyses are mothers education and day care center.

Table 6 – Distribution of otitis according to socio-demographic, peri-natal and behavioural characteristics and respective crude and adjusted odds ratio

	Otitis			OR Crude (CI 95%)		OR Adjusted (CI 95%)[1]
Determinants	n	%	p			
Age Mother (years)						
≤ 20	6	27.3		1	1	1
21- 30	159	40.1	0.079	1.78	(0.68 – 4.65)	2.42 (0.74 – 7.86)
31-40	95	33.8		1.36	(0.52 – 3.59)	1.71 (0.52 – 5.63)
>40	2	14.3		0.44	(0.08 – 2.60)	0.36 (0.03 – 3.81)
Mothers Education (years)						
0-6	52	40.9		1.58	(0.93 – 2.51)	1.96 (1.17 – 3.27)
7-9	59	34.9	0.070	1.22	(0.79 – 1.89)	2.46 (1.52 – 3.96)
10-12	89	42.0		1.65	(1.10 – 2.48)	2.13 (1.36 – 3.35)
≥13	61	30.5		1		1
Family Income						
0 – 1000 €	90	39.3		1		1
1001 – 1500 €	72	39.8	0.356	1.02	(0.69 – 1.52)	0.98 (0.64 – 1.52)
1501 – 2000 €	33	31.4		0.71	(0.43 – 1.16)	0.77 (0.44 – 1.34)
≥2001 €	35	33.0		0.76	(0.47 – 1.24)	0.86 (0.47 – 1.56)
Sex of child						
Male	139	38.9	0.285	1		1
Female	118	35.0		0.85	(0.62 – 1.15)	0.84 (0.61 – 1.15)
Birth weight						
<2500gr	28	32.2	0.357	1		1
≥2500gr	234	37.3		1.25	(0.78 – 2.02)	1.10 (0.74 – 1.98)
Gestational Age (weeks)						
≤37	52	34.4	0.526	1		1
>37	210	37.2		1.13	(0.78 – 1.65)	1.10 (0.75 – 1.62)
Breastfeeding						
No Breastfeeding	14	29.8		0.71	(0.36 – 1.42)	0.66 (0.32 – 1.36)
Until 4 Month	114	38.6	0.704	1.06	(0.73 – 1.53)	1.03 (0.70 – 1.51)
4 - 6 Month	44	36.4		0.96	(0.60 – 1.53)	0.88 (0.54 – 1.42)
>6 Month	75	37.3		1		1
Day-care						
Family	128	31.7	< 0.001	1		1
Babysitter	21	28.8		0.87	(0.50 – 1.51)	1.06 (0.60 – 1.87)
Day care center	109	47.2		1.93	(1.38 – 2.69)	2.77 (1.95 – 3.93)
Pneumococcal vaccine						
Yes	209	37.3	0.571	1.13	(0.78 – 1.65)	1.23 (0.82– 1.85)
No	53	34.4		1		1

1 – Adjusted for: mother's education and day care.

Table 7 – Distribution of otitis according to tobacco exposure and respective crude and adjusted odds ratio

Determinants	Otitis			Crude OR (CI 95%)		Adjusted OR (CI 95%) [1]
	n	%	p			
Maternal Tobacco Consumption						
Never	190	36.7		1		1
Pre-natal only	10	29.4	0.767	0.72	(0.34 – 1.54)	0.81 (0.37 – 1.75)
Post-natal only	14	33.3		0.86	(0.44 – 1.68)	0.80 (0.40 – 1.61)
Pre and Post-natal	41	38.7		1.09	(0.71 – 1.67)	0.98 (0.63 – 1.53)
Paternal Smoking						
No	152	37.6	0.567	1		1
Yes	95	35.4		0.91	(0.66 – 1.26)	0.86 (0.61 – 1.20)
Passive Maternal Smoking						
Non Smoker	203	36.4		1		1
Never smoked near the child	32	43.2	0.426	1.33	(0.82 – 2.18)	1.13 (0.68 – 1.89)
Smoked near the child	15	32.6		0.85	(0.45 – 1.61)	0.78 (0.40 – 1.51)
Passive Paternal Smoking						
Non Smoker	152	37.6		1		1
Never smoked near the child	45	37.8	0.935	1.01	(0.66 – 1.54)	0.97 (0.63 – 1.50)
Smoked near the child	33	39.8		0.68	(0.68 – 1.77)	1.04 (0.63 – 1.73)

1 – Adjusted for: mother's education and day care.

4. DISCUSSION

In this study, including children at 24 months of age, a high cumulative incidence of ARTI was observed, supporting the relevance of morbidity from acute respiratory diseases in children (otitis 36.6%, tonsillitis 27.2%, bronchiolitis 17.2%). Our findings are in accordance with the international literature, which states that ARTI, including OM are common illnesses in children[7,88,89,90]. In a study conducted in Norway, published in 2010, OM before 18 months of age was experienced by 32.7% of children[91]. A Greek study, published 2010, found a 29% of reported OM episodes in children with 12 month of age [26]. In Finland, a study from 2010, found that ARTI was present in 44% of children one to three years attending day care centers[92]. A study conducted in Norway (2000) found that URTI were common at the age of four years[93]. It was studied the prevalence of ARTI considering the occurrence in the previous month of the study and 7.1% of the children had OM and 7.5% experienced tonsillopharyngitis[93]. In the previous 12 months of the study, 9.5% of the children experienced more than one case of OM and 6.9% had more than one tonsillopharyngitis episode[93].

Nevertheless, the cumulative incidence of ARTI found in our study and in those recently conducted is lower than the reported by older studies, namely the Finnish studies. In 1987, one of these Finnish studies found that 56.7% of children before the age of 18 months had had at least one episode of OM, while 26.9% had had one or two episodes and 29.8% three or more[94]. Another study conducted in Finland found that the cumulative incidence of the first episode of OM up to the age of 12 months was 42.4% and the corresponding figures up to the age of 24 months, was 71.0%[95]. A USA five years cohort study observed, in 1995, a LRTI rate during the first 24 months of life[28].

Worldwide, more than 80% of children have developed OM at least once before three years of age[26]. This frequent illness among children represents the most common cause of physician visits for sick children and the major reason for antibiotics prescription in developed countries[26].

In the present birth cohort study, a significant association was found between ARTI (not including otitis) and the fact of children attended a day care center, mothers' education and with passive paternal smoking. Also, an independent effect was found for day care center attendance, mother's education on the development of otitis.

There is previous evidence that attendance at day care centers is an important factor contributing to the risk of developing upper and lower respiratory tract infections, during the first years of life, in accordance with the findings of various studies [6,26,92,93,96,97,98]. The Ninth International Research Conference on OM listed attendance at a day care center as an important risk factor for developing URTI including OM[99].

The prevalence of children attending a day care center in the studied sample was 32.4%, similar with the data from Eurostat about Portugal 32%[52]. The country with the highest percentage of children less than three years attending daycare centers was Denmark (73%), in contrast with Czech Republic and Poland which presented the lowest European rate (2%)[52]. The USA, United Kingdom (UK) and Finland were in the middle range with percentages from 30% to 40%, whereas Netherlands, Denmark, Belgium, Canada, and Norway had higher percentages (>40–70%)[99].

When comparing data of children taken care by their relatives with children attending a day care center, these last have a higher risk of developing ARTI [93,100]. It has been suggested that the number of contacts with other children is proportional to the number of ARTI episodes[93]. Because, transmission occurs more commonly in crowded conditions, the most plausible explanation for the increased risk of ARTI in children

attending a day care center is that there is a higher physical proximity between them which facilitates the transmission of microorganisms.

In our study children of mothers with a higher level of education, considering the level of education that mothers have reached throughout their lives, presented lower risk of ARTI and otitis.

This effect of maternal education on susceptibility of developing ARTI found in our study is consistent with others studies[26,93]. It has been described that socio-economic conditions are a risk factor for URTI[98]. The Ninth International Research Conference on OM stated that the greatest increase in the prevalence of early and recurrent OM was observed in poor children and those with less educated parents[99].

The level of mother's education can be considered an indirect indicator of socio-economic status, with a direct relation to material circumstances, working conditions and social prestige[47]. Usually mothers with a higher educational level have better working conditions, higher income, more information, better access to health care and all these conditions together lead to a higher capability of managing her health and their children´s health[100].

In our study 19.6% of mothers reported smoking during pregnancy which is similar to the prevalence described in the national health survey in regular smoking women at age of 25-34 years (16%) and at age of 35-44 (19.1%)[64]. A study conducted in Portugal (1995) found a prevalence of smoking women during pregnancy of 11.5%, which is lower than the prevalence found in the present study[101].

A prevalence of 11% was found in a Norwegian study (2008) regarding maternal smoke during pregnancy[102], in the USA (2004) a prevalence of 10% of maternal smoking during pregnancy was found [58].

There is evidence that smoking during pregnancy leads to a higher risk of LRTI in children and this risk is particularly high in early childhood[103]. The adverse health effects in children caused by exposure to environmental tobacco smoke have been known and children are primarily exposed inside their homes and by their parent's smoking[98,104].

Our results suggest that maternal smoking during pregnancy may be a risk factor for ARTI. In univariate analysis, it was found that ARTI is higher in infants of mothers who smoked during pregnancy and still smoke at 24 months of their children's age. In the multivariable analysis, the association remained positive but, no statistically significant differences were found when comparing with children that have never been exposed to their parents smoke. In this study, also no statistically significant association were observed between gestational smoke, consumption of tobacco by parents and ARTI.

However, a significant association was observed between children of smoking fathers that refer not to smoke near their children and respiratory tract infections.

It is possible that participants did not reported if they really smoked in the presence of their child, because it is social objectionable. This may introduce an information bias and explain the found association of children's exposure to second-hand smoke of fathers and ARTI.

In a meta-analysis, adverse effect of tobacco exposure on children's respiratory health was found with consistency for LRTI[105]. This association is very pronounced in children younger than two years, but diminished after the age of two, what can explain our results[59,105]. There are studies that described a higher incidence of OM in children exposed to maternal smoke during pregnancy[93,102]. However, an analysis of National Health and Nutrition Examination Survey III published in 2002 found that passive smoke exposure was not associated with an increased risk of ever developing an ear infection[106].

Also, in the present study no association was found between breastfeeding and ARTI, as it would be expected to happen according to the majority of studies, reduced number of studies that observed the same result[81]. A possible explanation could be related to the medium/long term effect of breastfeeding. The increased age of children, cessation of breastfeeding and degradation of maternal antibodies, influence children's susceptibility to infections as immune system gradually looses maternal antibody protection and starts to produce its own immunoglobulins[6,107].

Breastfeeding appears to reduce OM incidence in several studies[92,97]**.** The results of a study conducted in Czech Republic showed that breastfeeding can play a significant preventive role against OM when used for a period of up to 11 months[108], which is difficult to find in the present study because breastfeeding prevalence is very low at this age. A cohort study published June 2010 found that exclusive breastfeeding until the age of four months and partially thereafter is associated with a significant reduction of respiratory morbidity rates in infants until the age of 12 months, but it is recommended that effects of prolonged and exclusive breastfeeding on infectious diseases at older ages in industrialized countries should be studied[86], because this relationship has not been consistently demonstrated [6,109]. A cohort study conducted in Denmark (2008) described that breastfeeding is protective against illnesses only for the first year of life[6].

In contrast, a study, in north-American population, described that breastfeeding was not a protective factor for ear infections in children[106]. Also, a prospective multicenter study conducted throughout Western Europe found that respiratory infections occurred with similar frequency in breastfed infants and formula fed children [109].

The goals of *Healthy People 2010* for breastfeeding are an initiation rate of 75 percent and continuation of breastfeeding of 50 percent at six months and 25 percent at 12 months postpartum[110]. In this study, we find an initiation rate (ever breastfed) of 93.5% which is higher than the *Healthy People 2010* objective. The initiation rate is also

higher than the rate observed in a Portuguese National Health Survey conducted in 1999 (85%)[79]. A high initiation rate is observed but there is a sharpen drop in the percentage of children being breastfed at six months of life, as observed by other studies conducted in Portugal[79]. A cohort study conducted in Portugal, at the Maternity of Hospital Santa Maria, found that at discharge 91% of mothers were breastfeeding, 54.7% at the third month and 34.1% at sixth month[79].

Breastfeeding rates are higher than those found in the US survey of 2002[111], which showed that only 71% of American children have ever been breastfed[111].

The results are within the values found in southern European countries, with initiation rates around 80%, falling to 50% at three months and 25% at six months of child's life[112]. France has the lowest rate of breastfeeding initiation, 50%[99]. Poland and Belgium breastfeeding rate at six months of children's life are lower than 10%[99].

In contrast with day care center attendance, mothers education and exposure to second hand smoke from the father, no association was found between the perinatal variables such as birth weight, gestational age and ARTI at 24 months of age.

Prevalence in Portugal of low birth weight increased from 4.6% in 1980 to 7.6% in 2004[113]. In this study a prevalence of low birth weight of 12.1% was found which is higher than that described by the WHO for the European countries (6%)[114].
In Portugal, a decreasing trend in the prevalence of preterm birth was evidenced from 12.0% in 1990 to 6.7% in 2004[113], however, in this study a prevalence of preterm birth of 21,0% is found, as reported in many industrialized countries[115].

In a study conducted in Norway (2000) an association between low birth weight and the risk of OM in preschool children has been found[93]. Another study conducted in Norway, published 2010, a modest increase risk of having OM was found in children born

preterm[91]. It seems that preterm birth is more important than low birth weight when determining risk of having OM in early life[91].

Data presented at the Ninth International Symposium on Recent Advances on OM, showed that there was no increase in recurrent OM risk, for moderately low birth weight children (1500–2499 g) until the age of 24 months[99].

No significant association between birth outcomes (low birth weight and gestational age lower than 37 weeks) and risk of ARTI/OM is found in the present study.

Streptococcus pneumoniae is one of the leading causes of invasive pneumococcal diseases responsible for septicemia and meningitis, as well as non-invasive infections such as community-acquired pneumonia and acute otitis media[116].

The vaccination coverage of the National Immunization Programme in the North region of Portugal is high. Nevertheless, the pneumococcal vaccination was not included in the National Immunization Programme, the coverage in the sample studied is high (78.4%). In relation to pneumococcal vaccination no association was found with the risk of ARTI at 24 months of age.

Controlled trials have assessed the efficacy of the pneumococcal conjugate vaccine in reducing the incidence of invasive pneumococcal diseases caused by *S pneumoniae*, such as pneumonia, and clinical episodes of acute otitis media in healthy infants[97,117]. A meta-analysis published in 2009, showed a modest, although significant, efficacy of the pneumococcal vaccination towards prevention of all episodes of acute otitis media[117]. Recent studies showed that OM incidence has decreased following the introduction and routine use of 7-valent pneumococcal conjugate vaccine (PCV7) in children[97].

Our results are not consistent with these studies, but are in line with another trial of PCV7 in children with recurrent OM that found no beneficial effect on OM [118].

The lack of substantial benefit of pneumococcal vaccination for ARTI and OM in this population is likely to be due to a combination of factors[119]. The epidemiology of *Streptococcus pneumoniae* is changing since the introduction of the PCV7, non-vaccine serotypes are emerging[120]. Some replacement in pneumococcal carriage with nonvaccine serotypes has been reported since the release of PCV7[121].

Indeed, a reduction of all-cause pneumonia hospitalizations among USA children aged 24 months has been documented, and it has been associated to the introduction of routine PCV7 use[117].

Although there is no significant benefit observed in our study for children using PCV7, there are sufficient data and studies to recommend the use of pneumococcal vaccination[122].

No statistical difference was found when associating sex and ARTI or OM in the first 24 months of life. There are conflicting reports on the influence of infant gender on health outcomes. A study conducted in Norway, published 2010, found that OM was reported more often in boys than girls, as 5.4% of all boys experienced OM the first 6 months of life, versus 4.5% of the girls[91]. Various studies have shown that the risk of lower respiratory tract infections was increased for boys when compared with girls [44,96]. These results are not in line with our study, as no significant statistically differences are observed.

Strengths and limitations

This study is part of a prospective birth cohort, that includes some data collected before the occurrence of the outcome (for example: birth weight, gestational age and exposure to tobacco smoke during pregnancy) but for other variables (such as

children's exposure to secondhand smoke) are cross-sectionally collected, which gives an ambiespective design to the study.

This study has limitations that need to be taken into account when interpreting the results. The study's main limitation is that the outcome are reported by parents or relative, rather than documented by a physician. However, studies showing the reliability of parental reports, found good to excellent concordance between medical and parental reports[55,103,106]. A study conducted in Canada compared parents' reports with pediatricians' records about children health events, namely bronchitis, OM and birth weight, concluding that parent reports are acceptable for most research purposes and may be a better source for some health events[123].

The absence of association for variables such as breastfeeding, birth weight or gestational age could in part be explained by the fact of being characteristics that have occurred in a relatively distant period of time. We also could assume some statistical power limitations that could justify the absence of statistical significance between some of the evaluated exposures and outcomes.

One of the major problems in cohort studies is to accomplish a successful follow-up. For this reason we started by comparing the known characteristics of the two groups, 24 months participants and non participants. No statistical differences were observed for the following variables: birth weight, gestational age, sex of child and gestational smoke between the two groups of participants. Concerning the variables age of mother and mothers education statistical differences were found between the two groups. Among participants at 24 months mothers were older and more educated than non participants mothers, this fact may underestimate the observed cumulative incidence estimates.

The major strength of our study is being part of a larger population-based birth cohort, and infants were not selected according to their health status. The longitudinal collection of data is also a study strength. The assessment of exposure variables at delivery provided an opportunity to reduce the recall bias and improve the establishment of temporality, strengthening the validity of some of the current findings.

In conclusion, ARTI are highly prevalent, especially OM. The results support that attending a day care center and level of mothers' education are important risk factors for developing ARTI.

The results of this study are important in a public health perspective in order to understand the risk factors associated with ARTI and should be considered in future studies or actions to study or reduce ARTI. These study findings are mainly in consistence with the worldwide intervention to control ARTI, especially when it concerns the reduction of contacts of infected children attending a day care center. There is a need for intervention to increase the level of mothers' education and information to achieve a better health status for them and for their children.

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