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Pharmacoeconomic study based on cost-benefit ratio combined with a medicinal chemistry approach to favorable decision-making for Prevenar13 ® vaccination in southern Morocco

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Abstract

The primary objective of the Streptococcus pneumonia immunisation programme is to improve children's health by preventing hospitalisations and deaths through widespread vaccination. Active immunisation against pneumonia, invasive diseases and acute otites media caused by *Streptococcus pneumoniae* in infants and elderly children greatly improve the quality of their lives. In this respect, our Pharmacoeconomic and Pharmacoepidemiology study was conducted to investigate the cost benefit of the vaccination strategy to reduce monetary complications and morbidity related to streptococcal pneumonia as well as the additional costs of treatment and hospitalisation are avoidable by acting through the prevention strategy. In Morocco, 4,000 children under the age of 5 die every year from pneumonia, 15% of deaths are due to complications of meningitis, and one in three cases of acute otites media is due to pneumococcus. Among children under six months hospitalised for bronchitis in the paediatric ward, 73% were diagnosed with respiratory syncitial virus, while 26.1% of their peers aged over six months were diagnosed with adenovirus, and 10.5% of children under six months with bronchitis. Concerning 7.03% of patients hospitalised for bronchitis were exposed six times to influenza Virus A infection, while (6.03%) were subject to exposure to influenza Virus B infection.

Keywords: Cost benefit, Pneumonia, chemistry approach, New born, Pharmacoeconomic study

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1. Introduction

Every year, 4,000 children under the age of 5 die of pneumonia in Morocco, the leading cause of death in infants from the third month of life [1]. Pneumonia is an acute inflammation of the parenchyma of the lower respiratory tract caused by a microbial pathogen. While the clinical diagnosis is often straight forward, the aetiological diagnosis tends to be presumptive, based on radio-clinical aspects. Bacterial infections are generally primary. It should be noted that viral respiratory tract infections, such as influenza, may increase the subsequent risk of bacterial pneumonia. In particular, lower respiratory infections [2]. It is estimated that around 25% of deaths under the age of 5 are attributable to ARI in these countries. ARIs are responsible for 1/4 to 1/3 of deaths in young infants [3], almost all of which are linked to acute lower respiratory infections or lower respiratory tract infections, particularly pneumonia [4]. Diseases caused by *Streptococcus pneumoniae* are a public health problem throughout the world. In developing countries, most cases of bacterial pneumonia are attributable to *Streptococcus pneumoniae* infection, which is one of the main causes of meningitis, with febrile bacteraemia and otitis media being more popular manifestations. In Morocco, meningitis, particularly meningococcal meningitis, is a serious public health problem. A national programme to combat the disease has been put in place, with a strategy focused on monitoring meningococcal meningitis. This action has been directed towards exhaustive surveillance of all forms of meningitis, with a particular focus on the three most important bacterial forms (meningococcus, pneumococcus and Haemophilus

influenzae) [5]. There are several forms of meningitis, but bacterial forms are the most serious and can be caused by several germs, particularly *Streptococcus pneumoniae*, Neisseria meningitidis and Haemophilus influenzae type B [6]. It is estimated that almost a million children die from pneumococcal disease every year, most of them young children in developing countries.the development of a vaccine against 83 different serotypes responsible for the most serious forms of the disease [7]. The 7-valent pneumococcal conjugate vaccine received its first marketing authorisation in the United States in 2000 [8]. The serotypes it contains cover 65% to 80% of the serotypes associated with invasive pneumococcal disease in children in the United States and Western Europe. In the developed world, children under 2 years of age are the most affected by this disease. It should be added that the incidence of pneumococcal infections is accentuated in some places by the HIV/AIDS epidemic [9]. In Morocco, the PCV13 vaccine was introduced in 2010, and the new conjugate polysaccharide pneumococcal vaccine contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F [10]. Assessing the performance of the national programme for the control of acute respiratory infections in Morocco in children aged 0-59 months, estimates record more than 32,251children with a respiratory pathology [11]. Newborn survival rates have improved with scientific progress, particularly for premature infants, rates have recorded a decline from 21. 7 ‰ in 2011 to 13.6 ‰ in 2018 [12,13]. Retroactive analysis of 175 deaths out of 1,000 newborns hospitalised in an urban paediatric facility located in the south of Morocco in the Laâyoune region revealed a downward trend in neonatal mortality rates, of which 3.7% was attributed to prematurity and 1.1% to perinatal infection [14]. Premature births, complications of childbirth (asphyxia) and congenital malformations are the main causes of mortality in children under five [15], and 13.4 millions infants will be born prematurely (before 37 completed weeks of gestation) in 2020 [16], of which almost 900,000 died in 2019 [17]. Complications of prematurity are the main cause of mortality in children under the age of five. With regard to respiratory distress, it should be noted that maternal-foetal infection is more likely to cause distress in premature newborns, whereas placenta previa or retroplacental haematoma protect newborns against respiratory distress [18]. In adulthood, this burden weighs heavily in terms of complications and sequelae in premature babies, since a good number of births run a higher risk of anxiety, depression, neurological and behavioural abnormalities, as well as cardiopulmonary functional limitations, systemic hypertension and metabolic syndrome compared with their term-born peers [19]. In terms of factors, studies have identified a number of exposure factors consubstantial with the mother, such as multiple pregnancies, infections and chronic illnesses, such as diabetes and hypertension, as well as genetic factors [20]. Globally, the proportion of neonatal deaths among all children under 5 is still relatively low in sub-Saharan Africa (36%), which remains the region of the world with the highest under-5 mortality rate. In Europe and North America, where under-5 mortality rates are among the lowest of the regions targeted by the sustainable development goals, 54% of all deaths among children under 5 occur during the neonatal period. Among the causes of neonatal death, premature birth, complications during childbirth (birth asphyxia or total lack of respiration), infections and congenital malformations were responsible for most neonatal deaths [21]. Post-neonatal mortality in Morocco stood at 4.4 deaths per 1,000 live births in 2018 [22]. The risk of death for newborns aged between one month and one year in the country has decreased over the years studied. In comparison, the mortality rate was 14 deaths per 1,000 live births in 2004 (see figure 1) [23]. It should be remembered that poor quality neonatal care is responsible for 61% of neonatal deaths [24]. Furthermore, the main complication of acute respiratory infection is respiratory distress syndrome, which is generally triggered by a pulmonary surfactant deficiency in the newborn's lungs. Three quarters of these deaths could be prevented by routine interventions and a pharmacoeconomic cost-utility study comparing the costs of pneumonia and the consequences of vaccination strategies.

Pneumonia is the most serious infectious disease for children worldwide, killing more than 725,000 children under the age of 5 every year, 190,000 of whom are newborns, and running a significantly high risk of infection [25]. Worldwide, 13.4 millions babies were born prematurely at the beginning of 2020, i.e. 10% of newborns, compared with 0.14% in 2010, of whom almost a million died from complications due to their premature birth [26]. More specifically, preterm births run a higher risk of exposure to the morbidities and mortality associated with streptococcus pneumonia than their full-term counterparts, as they are exposed to maternal determinants that predispose to early-onset pneumonia in newborns, such as premature rupture of membranes and maternal fever, as well as other factors that predispose to late-onset pneumonia, including pre-lactation, oil instillation into the nose and milk suctioning, and maternal milk weaning [27] . Premature newborns remain vulnerable to numerous complications, including respiratory distress syndrome, cardiovascular disorders, and neurological conditions. These complications affect immature organs that are not yet prepared to support extrauterine life. Indeed, a significant rise in the incidence of respiratory distress syndrome (RDS) has been noted in neonates (NN), particularly affecting children with a birth weight > 2500 g [19]. Pneumococcal pneumonia accounts for approximately 95% of serious pneumococcal disease episodes and nearly 90% of pneumococcal-attributable deaths [28]. The availability of Prevenar13® pneumococcal vaccine against *Streptococcus pneumoniae* infection began in 2010 in Morocco, and marked a turning point in the endemic response, allowing a reduction in the use of non-pharmaceutical interventions to further protect children under one year of age against pneumonia, meningitis, febrile bacteremia and otitis media [29]. Despite the effectiveness of the new Prevenar13® vaccine marketed by Pfizer. Many newborns contract the infection, particularly in rural areas, due to a lack of information about the benefits of the vaccine. In Morocco, 4000 children under the age of 5 die each year from pneumonia, 15% of deaths from complications of meningitis are reported each year, and one in three cases of acute otitis media is due to pneumococcus (a disease that affects 60% of children before the age of 1 and 80% before the age of 3) [30]. Although the impact of vaccination against streptococcal pneumonia is frequently discussed, cost-benefit analysis provides a comprehensive account of the costs of the disease, including quality of life and costs for children under one year of age. Pneumonia can cause significant morbidity,

serious complications and even death. Vaccination is the most effective measure for preventing pneumonia/

1.1. Objective

The aim of this research is to compare the costs and benefits of the pneumonia vaccination program for the Moroccan population of children aged less than 18 months for the year 2023-2024.

2. Material and methods

This is a prospective multicentre study carried out between 1 January 2024 and 4 February 2024 in 3 paediatric departments in three regional hospitals in the various southern regions of Morocco : Guelmim-Oued Noun, Laâyoune Sakia l'Hamra, and Dakhla oued-Eddahab. The research involved 956 newborns, with a profile of newborns with acute lower respiratory infections. Nasopharyngeal aspirates were taken during respiratory physiotherapy sessions in all the patients included, and then sent rapidly to the laboratory. Diagnosis was also based on clinical symptoms and clinical examination such as severe cough, tachypnoea ≥60 c/min, wheezing, signs of respiratory difficulty and SpO2 ≤90% and abnormal lung auscultation, as well as radiological evidence of acute respiratory infection, where radiological assessment Was requested. Nasopharyngeal secretions were collected from children enrolled in this study, using a flocked nasopharyngeal swab, based on the standard technique, and then immersed in viral transport medium. Distal respiratory samples were taken from intubated children hospitalised in paediatric intensive care units. Samples were processed as soon as they were received in the microbiology laboratory for aetiological diagnosis. On average, results are available within two hours. This exploratory study estimates the economic evaluation of the cost-benefit type of the streptococcal pneumococcal vaccine of the vaccination program against preventable diseases in children under 18 months. The university hospital center of the southern region of Morocco in Laâyoune runs two hospital centers : the regional hospital center Moulay El Hassan Ben El Mehdi hospital as well as the Hassan II specialty hospital. The university hospital center also supervises the network of primary health care where newborns are vaccinated against streptococcal pneumonia. A population-based, age-structured economic model was used to conduct a cost-benefit analysis of S. Pneumoniae vaccination. The model used separate decision trees for each disease (pneumonia, meningitis and febrile bacteremia; otitis media), to project the updated number of vaccinated individuals, number of disease cases and medical costs direct and indirect (US$ 2024) over a period of one year. Benefit-cost ratios (BCRs) and net present values were calculated for two primary analyzes comparing current vaccination coverage versus no vaccination coverage. We conducted a model-based cost-benefit analysis of the Canadian Streptococcus pneumonia vaccination programme. We used an epidemiological model to estimate the number of symptomatic cases of pneumonia and deaths in the presence and absence of vaccination. The median, lower and upper 95% credible interval values of the results of 100 model simulations were used to estimate the direct and indirect costs of illness, including the value of health. We used a societal perspective and a discount rate of 1.5%). The analytical basis used to determine the value of the programme is benefit-cost analysis. We will identify and evaluate all the economic costs and benefits for a one-year period. We will also compare the costs associated with the health care system for vaccinated people and those for unvaccinated people, and then relate this difference in costs to the cost of vaccination.

3. Results

Pneumonia occurs when the normal defence mechanisms of the lower respiratory tract (mechanical and anatomical barriers, mucociliary activity, phagocytic activity, humoral immunity and cell-mediated immunity) ; deteriorate and become overwhelmed by pathogens, whose proliferation triggers immune and inflammatory processes, resulting in the accumulation of fluid, white blood cells and cellular debris in the alveoli. This can lead to reduced lung compliance, increased lung resistance, alveolar collapse and imbalance in lung perfusion ventilation, which can cause symptoms and signs of pneumonia. As the *Streptococcus pneumoniae* vaccination programme is compulsory, part of the target population is not vaccinated, given that it reduces the risk of infection in children under 5 years of age by 80 to 90%. The analytical basis used to determine the value of the programme is a benefit-cost analysis. The aim of the study is to identify and compare the costs associated with the care provided by the healthcare system for vaccinated and unvaccinated people, and then to relate this difference in costs to the cost of vaccination. In France, pneumococcal vaccination of infants has reduced the number of invasive pneumococcal infections by 48% in infants under 2 years of age and by 16% for all ages combined since the pre-vaccination period (before 2003). The incidence of invasive infections has fallen from 32.7/100,000 in the pre-vaccination period (8.8 meningitis and 24.0 bacteraemia per 100,000) to 24.3 invasive infections per 100,000 children under the age of 2 in 2019 (7.1 meningitis and 17.1 bacteraemia per 100,000 children) [30]. The herd immunity obtained with this conjugate vaccine explains the moderate reduction in invasive infections observed in all age groups. Vaccine efficacy varies, but is estimated at over 70% in most studies (Fig. 2). It is particularly high for the serotypes contained in the 7-valent and 13-valent vaccines (>90%), but is weakened by the phenomenon of serotype replacement, which is closely monitored by surveillance systems for invasive pneumococcal infections [31]. Finally, vaccination has also led to a reduction in the rate of carriage and infection with antibiotic-resistant pneumococci. The efficacy of vaccination has been well established, but 99% coverage does not exist, hence the need to encourage target populations to be vaccinated in order to avoid hospitals being overcrowded with cases of rapidly transmitted pneumonia [32].

3.1. Cost-benefit analysis of the Prevenar13 vaccine ®

3.1.1. The incidence or attack rate

In order to measure vaccine efficacy in the field, the incidence rates (attack rates) of the disease among vaccinated and non-vaccinated individuals are calculated, and the percentage reduction in the attack rate among vaccinated individuals compared with non-vaccinated individuals is determined. The basic formula is : EV= TANV-TAV/TANV where EV represents vaccine efficacy expressed as a percentage, TANV the attack rate of the disease among vaccinated individuals [33].

3.1.2. The hospitalisation rate

The hospitalisation rate represents the number of children hospitalised because of pneumonia in each age group of children under five, compared with the number of people in each group, to determine the cost-benefit of vaccination against pneumonia (Fig.3).(Bronchiolitis, Severe bronchiolitis with respiratory distress, Pneumonia, Pertussis, Influenza in immunocompromised children).to calculate the effectiveness of the vaccine in preventing hospitalisations, we calculate the difference between the hospitalisation rate for vaccinated children and the hospitalisation rate for non-vaccinated children, in order to determine the effectiveness rate in preventing deaths. Epidemiological measurement of the frequency of disease is of particular importance for medico-economic evaluation [34].

3.1.3. The genetic approach nucleic acid-based vaccine

A medicinal chemistry approach to the development of glycoconjugate vaccines is enabled by accelerated access to AGA-defined oligosaccharides [35]. Minimal protective glycan epitopes are identified using homogeneous synthetic oligosaccharides that constitute one or more repeating units of bacterial CPS. Glycoconjugates containing such synthetic antigens have already been individually tested for their antigenicity, immunogenicity and protective effects in animal disease challenge models and have been shown to be effective in some cases [36]. The objective was to expand vaccination coverage against S. pneumoniae by including conjugates of serotype antigens (Fig. 4). Note that the objective of vaccination coverage against S. pneumoniae is to include conjugates of serotype antigens (Fig. 5) currently absent from marketed vaccines, such as ST2 and ST8 in the case of Prevnar13 [37]. Among children under six months hospitalized for bronchitis in the pediatric department, 73% were diagnosed with respiratory syncytial virus, while their peers aged over six months 26.1%, concerning adenovirus 10.5% of children aged under six months suffering from bronchitis. Concerning 7.03% of patients hospitalized for bronchitis were exposed six times to influenza Virus A infection, while (6.03%) were subject to exposure to influenza Virus B infection. Which relates to children suffering from human parainfluenza virus in children less than six months old were respectively exposed twice (2.01) than their peers aged more than six months (1.01). Regarding children hospitalized for Pneumonia Overall, the Respiratory syncytial virus was associated 13 times with Pneumonia as the most frequent reason for hospitalization, as well as for adenovirus, children over one year old were exposed eight times than children aged over six months. Regarding the association between exposure to Pneumonia and respiratory syncytial virus was also significant at 95% ($p<0.001$), as well as for the association of influenza Virus A infection as well as influenza B infection, the association is significant at 95% ($p<0.001$). Among children under six months hospitalized for bronchitis in the pediatric department, 73% were diagnosed with respiratory syncytial virus, while their peers aged over six months 26.1%, concerning adenovirus 10.5% of children aged under six months suffering from bronchitis. Concerning 7.03% of patients hospitalized for bronchitis were exposed six times to influenza Virus A infection, while (6.03%) were subject to exposure to influenza Virus B infection. Which relates to children suffering from human parainfluenza virus in children less than six months old were respectively exposed twice (2.01) than their peers aged more than six months (1.01). Regarding children hospitalized for Pneumonia Overall, the Respiratory syncytial virus was associated 13 times with Pneumonia as the most frequent reason for hospitalization, as well as for adenovirus, children over one year old were exposed eight times than children aged over six months. Regarding the association between exposure to Pneumonia and respiratory syncytial virus was also significant at 95% ($p<0.001$), as well as for the association of influenza Virus A infection as well as influenza B infection, the association is significant at 95% ($p<0.001$)Regarding the co-infection of respiratory pathogens in children, the study revealed that the correlation between respiratory syncytial virus and parainfluenza is of medium intensity (R: 0.14), in addition, the rhinovirus is correlated by to adenovirus (R:0.5), as well as with covid-19 (R:0.7). Regarding the human parainfluenza virus, it is strongly correlated with human rhinovirus (R : 0.6), concerning the correlation between the respiratory syncitial virus and influenza A viruses, the correlation is of medium intensity (R : 0.34) with the influenza A virus, as well as for the influenza B virus (R : 0.41).

3.2. Economic evaluation of the program

Economic evaluation can be defined as the search for indicators allowing those who implement them to assess the positive and negative effects of a project or program from the point of view of society in relation to economic and social objectives defined in advance [38]. The essential purpose of cost-benefit analysis is to measure all the costs and benefits of a Project. The basic principle of choice of this evaluation depends on the social benefits being greater than the value of the costs. The objective of cost benefit analysis is to measure the relative value of potential projects with a view to efficient allocation of resources. The main problem of this method in the field of health is the valuation in monetary terms of the net benefits. The main drawback of the approach is the need to evaluate human lives and quality of life in monetary terms. This cost benefit approach allows the economist to provide the decision maker with the decision element. The costs and benefits are different from the costs and products of the financial analysis, since the evaluation of the costs and benefits requires that we take into account the effects of customer surplus and the producer's rent as well as the real positive and negative external effects [39]. As long as the objectives of political action are precise, the benefits and costs of a project will be identified and evaluated in relation to these. Any reduction in economic scarcity being considered as an advantage while any increase in scarcity as a cost [40]. The function of cost-benefit analysis is not to dictate the decision but to help the political process identify projects that could be uneconomic and point out projects that are clearly in the public interest. Public health. In the health sector, to estimate human life and the demand for health care, some economists propose two main approaches : the human capital approach and the willingness to pay approach [41]. Knowing that the primary objective of any pneumonia immunization program is to improve the health of taxpayers by avoiding hospitalizations and deaths. This improvement can be measured by the reduction in morbidity and mortality, the years of life gained or the improvement in quality of life. Determining the degree of mortality or morbidity caused by influenza is not easy in the as the population targeted by this

program has very fragile health, most often characterized by respiratory or heart diseases.

3.2.1. Direct costs

Ideally the analysis should take into account direct and indirect costs and intangible costs. The cost benefit analysis of the pneumonia vaccination program is designed from a societal perspective. Remember the hospitalization costs avoided, the consultation costs avoided by preventing pneumonia. All costs are recorded relative to the current situation in current dollars. The direct cost of the immunization program includes the resources used to purchase vaccines; vaccine administration, program management, vaccination and treatment of side effects. the analyzes carried out are carried out without updating given that this program is annual and is started again each year Since the duration of the pneumonia vaccine is less than a year.

3.2.2. The cost of purchasing Prevenar13® vaccine

The administration cost is estimated at 50MAD per dose administered, this cost includes the equipment used, the work of the nurse, the recording of the vaccination act. Obviously, administration costs are estimated. There is no new money budget.

3.2.3. Program management cost

It is estimated at 3% of the cost of purchasing vaccines by the general directorate of public health.

3.2.4. Cost of avoided hospitalizations and consultations (direct public financial benefits)

The analysis of the improvement in the state of health of society and the saved healthcare costs were carried out between a vaccinated population and an unvaccinated one. All studies and research carried out at the national level conclude that vaccination of children under 18 months of age is beneficial for society and the government. An analysis of avoided hospitalization costs = $19,207,871.6. Consultation costs avoided=218,570. In Morocco, children under 18 months of age are at risk of exposure to streptococcal pneumonia. With an attack rate varying between 23% and 8%, the effectiveness rate varied from 72% to 91% [42]. The hospitalization rate was 5%, comparing the vaccinated and unvaccinated group, they concluded that the program was beneficial to society. A clinical study which consists of comparing the economic benefits of the vaccine between vaccinated children and unvaccinated children. The vaccine effectiveness rate varied between 82% and 93%. The vaccine prevented hospitalizations due to pneumonia and its complications by between 56% and 73% [43]. The results obtained showed that the total cost of the overall charges attributed to the neonatology unit amounts to 3255432.415 MAD, or on average 6213.36 MAD per patient and 686.36 per day of hospitalization. These expenses are mainly composed of 48% in the form of administrative expenses, 25% of labor expenses, 14% of consumable expenses and 7% of depreciation expenses of biomedical equipment. The analysis of these results revealed that the cost of one day of hospitalization of the newborn in the neonatology unit is higher compared to national pricing (the daily rate of the incubator: During the first 10 days = 350 MAD /day from the 11th day = 200 MAD /day).

3.2.5. Evaluation of gains in healthy life expectancy

The willingness to pay for a gain in QALY (Quality adjusted life years) is positively determined by 2 factors, namely wealth and life expectancy gain, and the other two which determine negatively are the state of health and the possibilities of substitution of inter-temporal consumption. If the wealth of the individual changes, their marginal valuation of the benefits and the cost of marginal self-protection will change, these changes will partly affect the marginal expenditure in QALYs and the willingness to pay for quality additional life. To estimate the QALY, we were inspired by the results of an analysis that focuses on improving health care, they estimated the QALY value for pneumonia at 1.84 [44]. Pneumoniae is a leading cause of pediatric hospitalizations, primarily in children younger than 2 years. Hospitalization affects the quality of life of children under the age confirmed by the diagnosis S. pneumoniae at the time of their stay in the pediatric department. The dimensions of quality of life most affected and calculated in utilities. Caregivers completed the EQ-5D questionnaire, composed of a descriptive system (evaluating 5 dimensions of children's quality of life) using the visual analog scale (EQ VAS). Utility loss and loss of quality-adjusted life years (QALYs) were calculated. Utilities vary between 0.17 and 1 in the descriptive system and between 0.33 and 1 in the descriptive system and 0.33-1 (median 0.86) in the EQ VAS, with a utility loss of 0. 14 (IQR: 0.1-0.2) [45]. The calculated QALY loss reached a median of 2.45 × 10-3 (IQR: 1.37 × 10-3-4.56 × 10-3) and was not influenced by children's age or final clinical diagnosis (QALY loss for bronchiolitis: 2.74 × 10-3pneumonia: 1.84 × 10-3 bronchitis: 1.78 × 10-3 statistically significant differences). Moderate agreement between the descriptive system and the EQ VAS was observed (Spearman's rank correlation coefficient = 0.057, $p < 0.05$).

3.2. 6 The cost of time during vaccination

Time is considered a rare commodity, and therefore has value for economic analysts. any economic evaluation of a project involving, for certain people, a saving of time or consumption of time must take this into account. The value of time lost obviously comes from the alternative uses to which it can be employed with regard to this program, the cost of time, it is significant as long as vaccines for children under 18 months are scheduled according to a weekly vaccination schedule. To measure time, we use as a valuation indicator the maginal wage rate representative of the value of the marginal product. The value of time saved by a program will be: Time lost* wage rate=Value of non-produced goods [46].

4. Discussion

The present epidemiological study highlighted the prevalence of respiratory infections in hospitalized newborns with Streptococcus pneumonia, respiratory syncytial virus was prevalent (13%), with regard to adenovirus in children less than 6 months old. reached (0.13%), the prevalence reached (0.4) in children with enterovirus//rhinovirus hospitalized for Pneumonia as the reason for hospitalization, as well as for human parainfluenza virus, the prevalence recorded (3 %) [46].

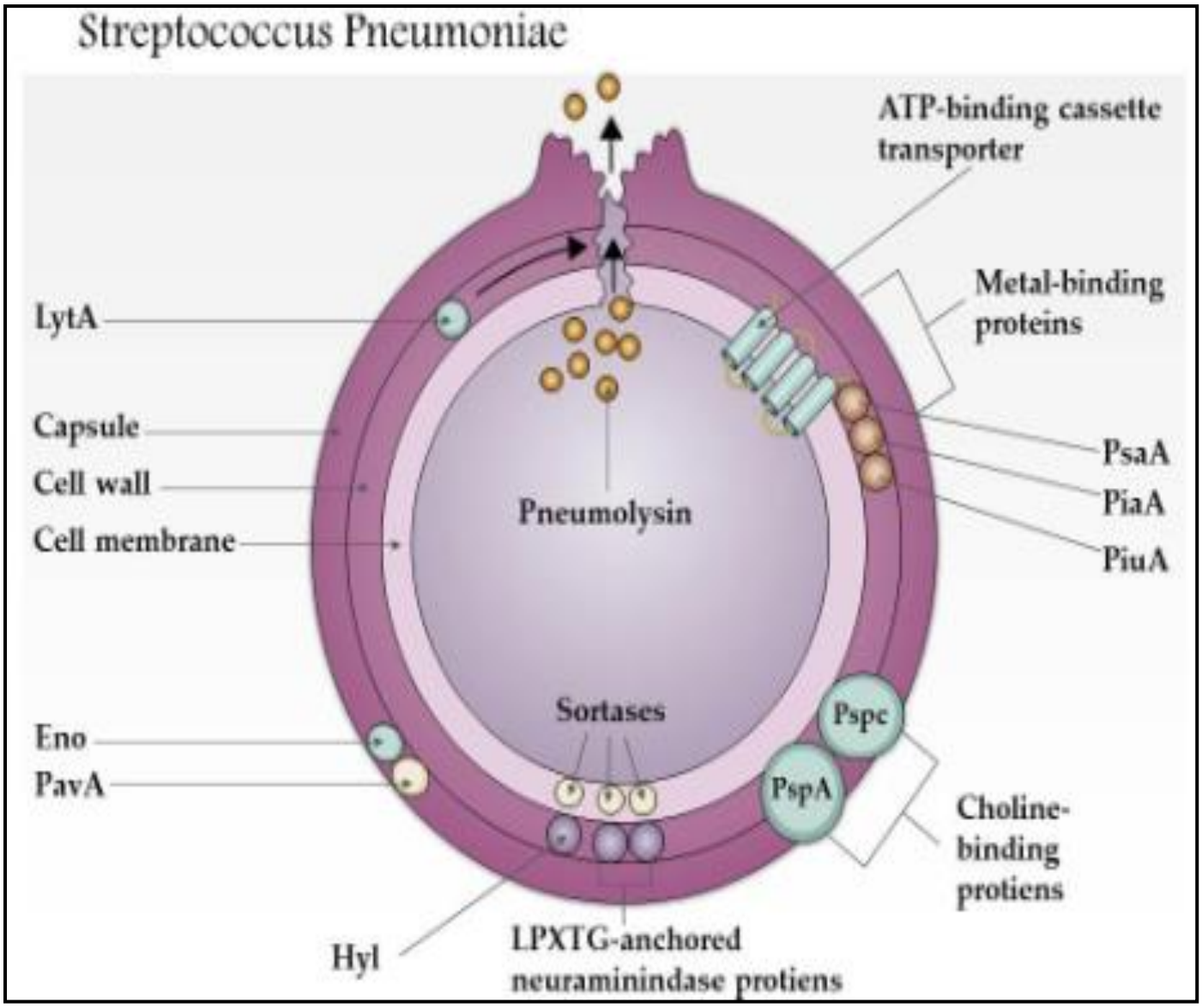

Figure 1 : *Streptococcus pneumoniae* medical images

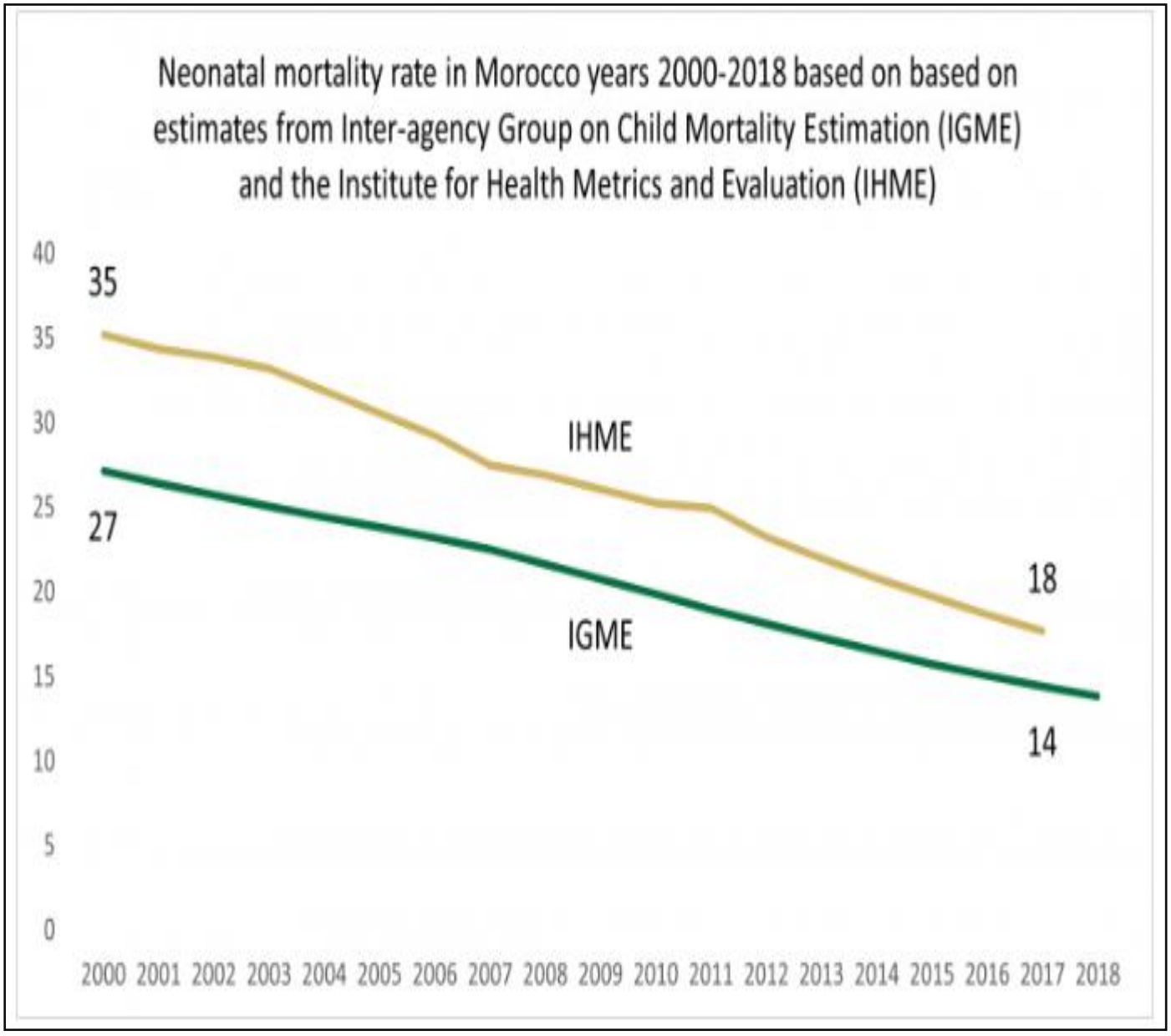

Figure 2 : Neonatal mortality rate in Morocco based on inter-group estimates

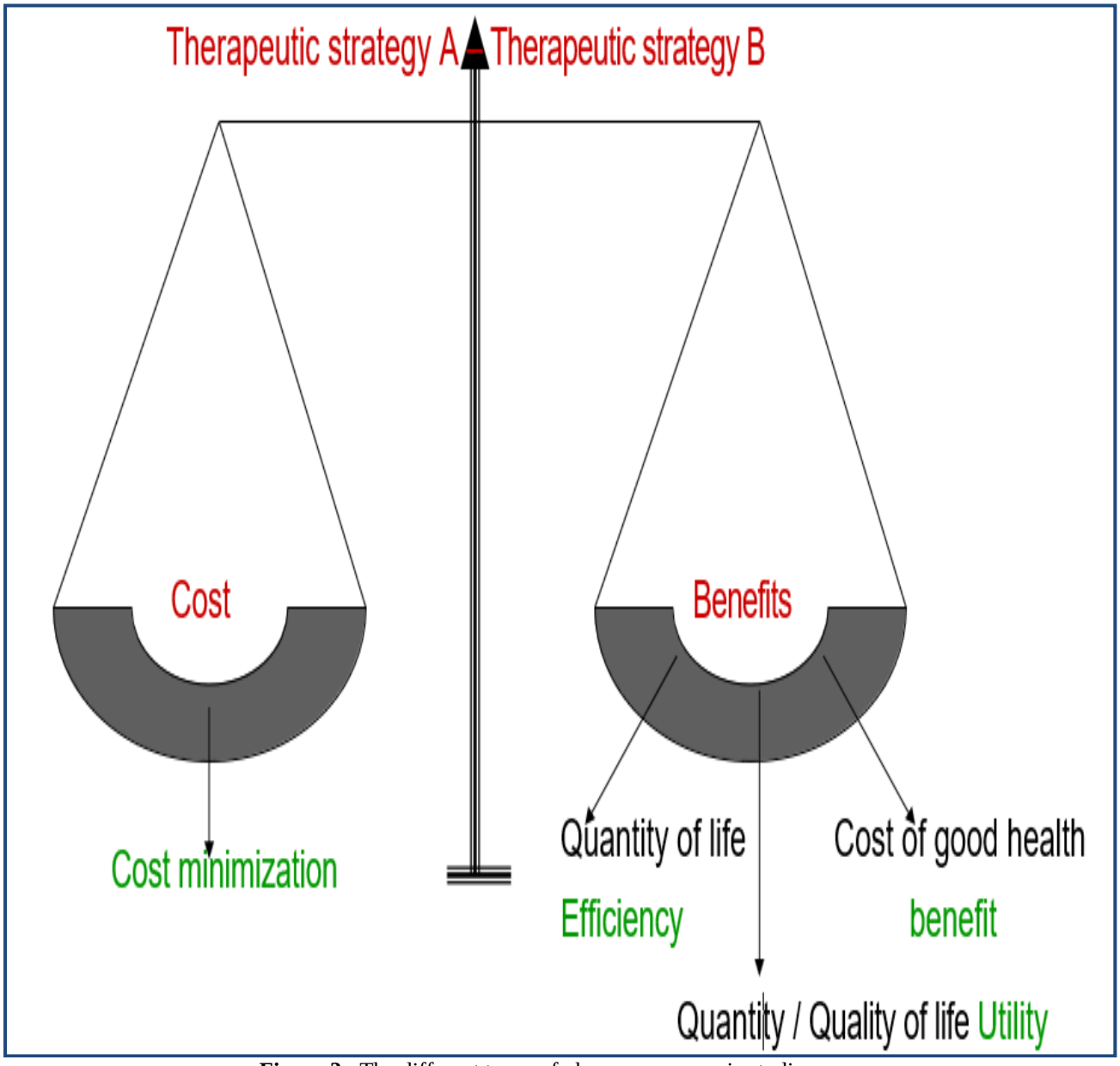

Figure 3 : The different types of pharmacoeconomic studies

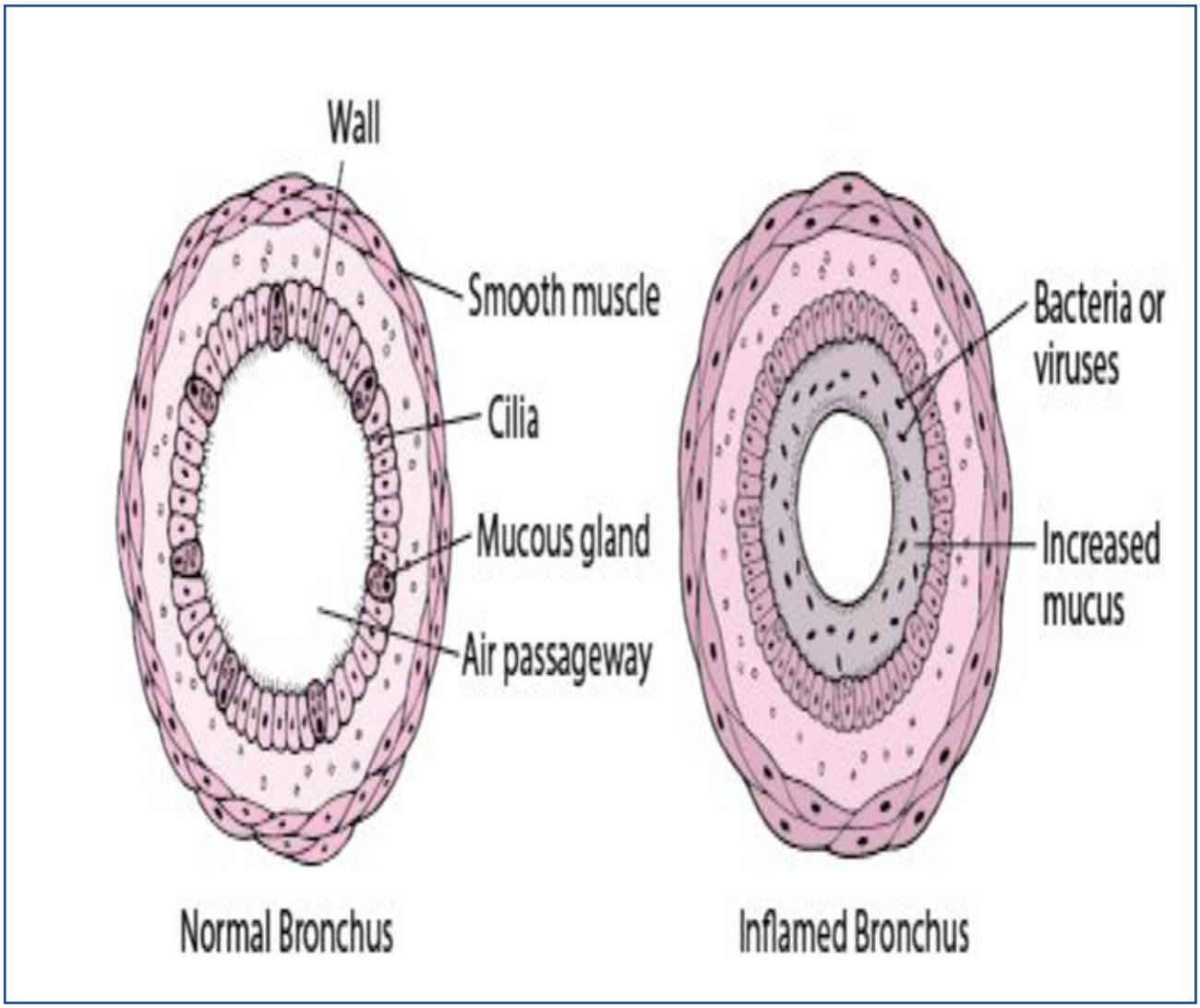

Figure 4 : Inflammation of the trachea and airways

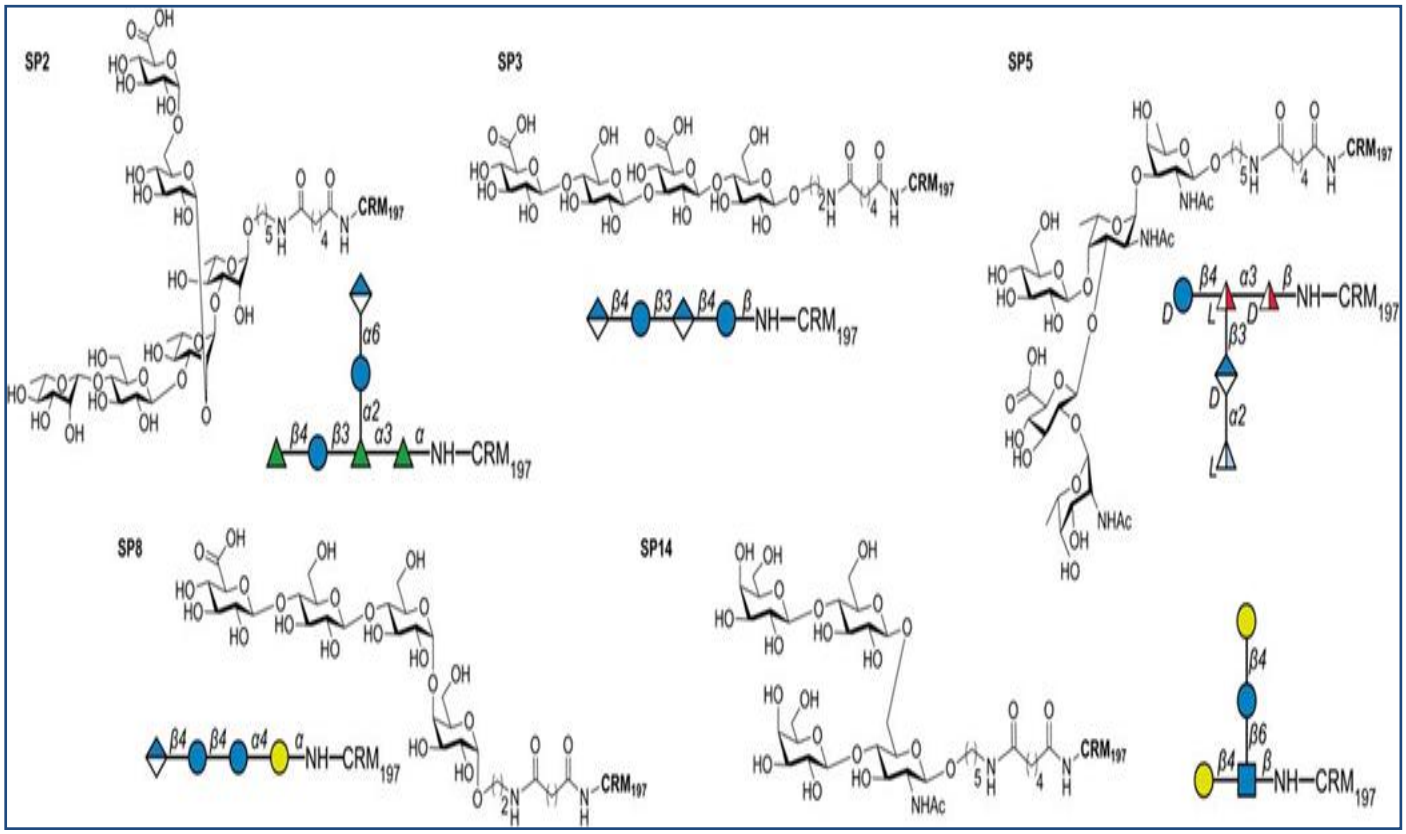

Figure 5 : The Medicinal Chemistry Approach in Inducing Higher Levels of Protective Antibodies

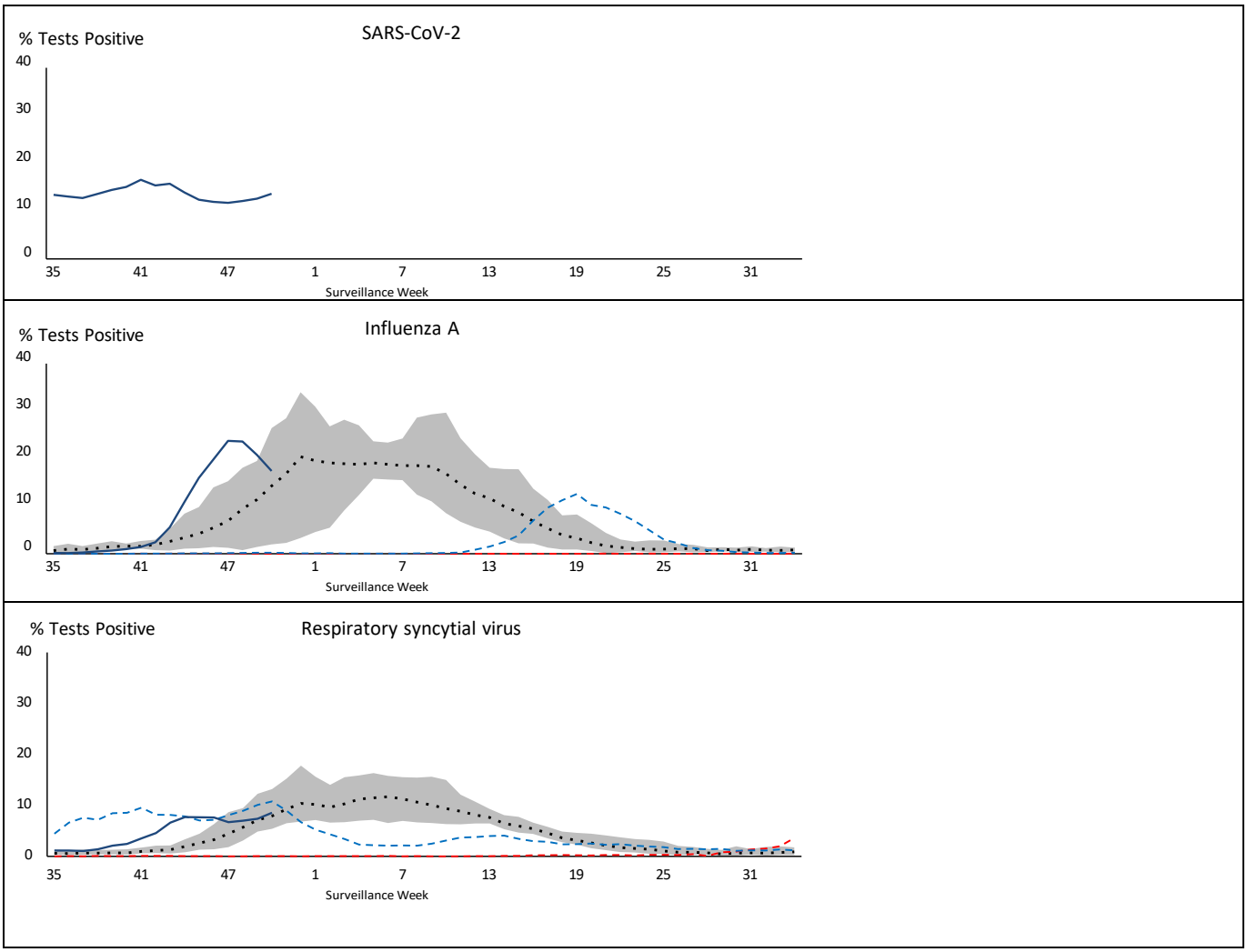

Figure 6 : Positive tests for severe acute respiratory syndrome coronavirus 2, influenza and respiratory syncytial virus (%)

Table 1: Prevalence of co-infection of respiratory pathogens in children at south of Morocco

	VRS	AdV	RhV	EntV	VI	VPI	MPVh	CoV	Inf A	Inf B
VRS	38									
AdV	13	2								
RhV	2	5	1							
EntV	4	4	3	1						
VI	14	5	0	0	1					
VPI	8	0	0	0	1	3				
MPVh	15	3	2	0	0	2	2			
CoV	0	1	0	0	0	0	0	0		
Inf A	14	0	0	0	0	1	5	0	0	
Inf B	1	0	0	0	0	0	0	0	0	0

VRS : Respiratory Syntical virus, AdV : adenovirus, Hmpv : human metapneumovirus, RhV : Rhinovirus VPI : parainfluenza virus, VI : Influenza virus, InfA : influenza A : InfA, Inf B : influenza B, CoV : coronavirus

Table 2 : Prevalence of viruses detected by type of respiratory infection and age of patients by type of infection

	Bronchiolitis (n = 199)			Pneumonia (*n* = 93)			*n= (223)*		
	Age range			Age range			Age range		
	1–6month (*n* = 147)	> 6 months (*n*= 52)		1–6 month (*n* = 40)	>6months (*n*=53)		1–6 month (*n* = 187)	>6months (*n=105*)	
RSV	57	11	$< 10^{-3}$	13	8	0,001	32	12	$< 10^{-3}$
AdV	21	15	$< 10^{-3}$	7	12	0,5	19	33	$< 10^{-3}$
RhV	21	13	0,023	5	11	1	45	14	0,035
EntV	8	2	0,19	2	5	0,21	2	29	0,59
VI	6	3	0,76	3	2	0,47	3	4	0,17
VPI	5	4	0,1	1	3	1	2	6	0,072
HPIVs	4	2	0,001	3	1	1	0	2	0,008
CoV	3	1	1	2	1	0,42	4	1	0,23
VIA	14	35	0,001	6	5	0.001			
VIB	12	9	0.001	3	6	0.005			
Total	147	52		40	54		187	105	

The association is significant at 95% ($p<0.001$), the results corroborate with a survey of prevalence of respiratory viruses among pediatric patients with acute respiratory diseases in Malaysia, the study involved 23,000 pathogens were detected by multiplex PCR. The five predominant respiratory pathogens detected in this study were enterovirus/rhinovirus (6,837/23,000; 29.7%), followed by influenza virus infection (5,176/23,000; 22.5%), RSV (3,652/23,000; 15.9%), adenovirus (2,637/23,000; 15.9%). 11.5%), and parainfluenza virus (2333/23000; 10.1%); Other frequently less detected respiratory pathogens include hMPV (819/23,000; 3.6%) and Mycoplasma pneumoniae (338/23,000; 1.5%) [47]. Remember that the main complication of acute respiratory infection is respiratory distress syndrome, which is generally triggered by a pulmonary surfactant deficiency in the lungs of the newborn. In particular, acute respiratory syndrome is a stereotyped response to various etiologies [48]. It progresses through different phases, starting with alveolar-capillary damage, a proliferative phase characterized by improvement in lung function, healing, and a final fibrotic phase signaling the end of the acute disease process [49]. Pulmonary epithelial and endothelial cell damage is characterized by inflammation, apoptosis, necrosis, and increased alveolar-capillary permeability, leading to alveolar edema and proteinosis. Alveolar edema, in turn, reduces gas exchange, leading to hypoxemia. One of the characteristics of the lesions seen in ARDS is that they are not uniform [50]. Certain segments of the lung may be more severely affected, leading to a decrease in regional lung compliance, which classically affects the bases more than the apexes [51]. A study based on the analysis of the cost of respiratory distress at the pediatric department, conducted estimated expected costs of an initial hospitalization per uncomplicated surviving infant with RDS were estimated at $101,867 for infants weighing 500 to 1,000 g; $64,524 for infants > 1,000 to 1,500 g; and $27,224 for infants weighing more than 1500 g [52]. Regarding the analysis of the cost structure by resources, studies have shown that the main expenditure item corresponds to consumable costs which represent 48% of overall costs, then labor costs which constitute 25%. of overall expenses while administrative costs and equipment depreciation represent respectively only 14% and 7% of overall expenses [53]. In fact, the salary costs of staff and in particular medical staff in the present study constitute the highest expenses, this is in agreement with the literature which shows that personnel expenses often constitute more than two thirds of hospital expenses [54]. And also joins the results of Moroccan studies; a study carried out on the analysis of the costs of the maternity ward of the Provincial Hospital Center Hassan I of Tiznit and the other on analysis of the costs of the hemodialysis session in the hemodialysis center of CHP Med V of Meknes which show that the Salary costs represent the first item of expenditure [55].

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