Epidemiology of Respiratory Infections

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The relationship between living disease agents—viruses, bacteria, fungi, and parasites—and their human or animal hosts can be studied at different levels. Biologists and biochemists analyze this relationship at the molecular and cellular levels, and are constantly making advances in knowledge about the pathogenesis of infections, as well as diagnosis and control through use of vaccines and medicines. Clinicians play the leading roles in the study and application of advances in individual curative medicine.

Epidemiology is the study of health at a human population scale, including transmissible and nontransmissible diseases. It also considers diseases that affect animals. It analyses factors depending on the agent, host, and environment that come into play in the population's health. Its contribution to the health field can be summarized as the following goals:

1. *Collaboration with clinical and laboratory diagnosis*: Epidemiology functionally defines suspicious and confirmed cases, using specific laboratories with validated techniques.
2. *Prediction of the appearance tendencies of infectious and noninfectious diseases*: Epidemiology provides a record of information and an appropriate collection of samples.

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   (a) *Impact*: Epidemiology describes mortality, morbidity, life-years lost through death or disability, and other parameters to measure the impact of different agents; it also predicts the appearance tendencies of infectious and noninfectious diseases.
   (b) *Pathogeny*: Epidemiology analyses the successive stages of disease, considering the source, transmission mechanism, portal of entry, human dissemination, defense mechanisms, and elimination from the community.
3. *Proposition and evaluation of measures of control*, including resource planning.
   (a) *Prevention*: These measures include (i) vaccines, (ii) education, (iii) the environment, (iv) biosecurity, (v) chemoprophylaxis, and (vi) passive immunization.
   (b) *Treatment*: This involves application of antibacterials, antivirals, antifungals, and other support measures such as oxygen treatment or mechanical ventilation.

Viral Respiratory Infections

Several indicators illustrate the big global impact that acute respiratory infections (ARIs) have on public health, through morbidity and mortality. According to the World Health Organization (WHO), respiratory infectious diseases take first place in the ranking of the burden of disease measured by years lost through death or disability (disability-adjusted life-years (DALYs)). Lower respiratory tract infections represent the third leading cause of death in the world, after cardiac and encephalic vascular illnesses; however, in countries of low economic status, they take first place.

Many regional or global estimates have identified acute respiratory infections as a primary cause of ambulatory consultations, hospitalizations, and deaths. In Chile, they take second place and third place in the leading causes of death in children and adults, respectively. Furthermore, several studies point toward them as the main causes of ambulatory consultations and absenteeism from both school and work. Their seasonal form of appearance and high infectivity place viruses as being responsible for the majority of acute respiratory infections. According to post-neonatal mortality estimates, lower respiratory tract infections cause 20% of deaths, with respiratory syncytial virus (RSV) and influenza virus being most common (9.5%). Advances in viral diagnosis have confirmed the participation of viruses in respiratory pediatric pathology, with frequencies that go from more than 50% (if they compromise the lower respiratory tract) to 90% (if they affect the upper respiratory tract). In adults, the scenario of upper respiratory tract infections is similar, but in lower respiratory tract infections a predominance of bacterial etiologies has been described. However, application of molecular viral diagnosis shows significant participation of respiratory viruses in lower respiratory tract infections. This fact acquires more relevance when considering the aging of a population.

Several viruses are included in the group of "respiratory viruses" because they have the respiratory system as a target organ. Nevertheless, other viruses can also compromise the respiratory system while a systemic infection takes place (measles, chickenpox, enterovirus, hantavirus), especially in immunocompromised individuals (cytomegalovirus, herpesvirus, shingles). Furthermore, studies always show an important group of cases without a proven etiology, although the number of such cases has diminished with the application of molecular diagnosis techniques because many potentially pathogenic agents are now being detected or discovered (Table 28.1).

The clinical manifestations of viral respiratory diseases vary from asymptomatic cases to fatal infections, with several intermediate scenarios. Some viruses tend to produce infections mainly in the upper respiratory tract (rhinovirus, coronavirus, adenovirus), while others can similarly compromise the lower respiratory airways, with variable severity (adenovirus, RSV, metapneumovirus, influenza, and parainfluenza). In general, it is an accepted fact that any respiratory virus can compromise one or several levels of the

Table 28.1 Main causes of disease worldwide (World Health Organization 2004)

	Disease or injury	DALYs (millions)	Total burden (%)
1	Lower respiratory tract infection	94.5	6.2
2	Diarrhea	72.8	4.8
3	Unipolar depression	65.5	4.3
4	Cardiac ischemia	62.6	4.1
5	HIV/AIDS	58.5	3.8
6	Encephalic vascular disease	46.6	3.1
7	Prematurity	44.3	2.9
8	Asphyxia and neonatal trauma	41.7	2.7
9	Traffic accidents	41.2	2.7
10	Neonatal infections	40.4	2.7

AIDS acquired immunodeficiency syndrome, *DALYs* disability-adjusted life years, *HIV* human immunodeficiency virus

Table 28.2 Predominant viruses in the respiratory system

Virus	Varieties: types, serotypes, genotypes, and other
Rhinovirus	Species A, B, and C: >101 serotypes
Coronavirus	Alpha: 229E, NL63; beta: OC43, HKU1, SARS, MERS
Respiratory syncytial virus	A and B groups; genotypes and lineage
Metapneumovirus	A and B groups; genotypes
Adenovirus	55 serotypes
Influenza	Types A, B, and C; subtypes A H1–3, N1–2; several strains
Parainfluenza	4 serotypes
Bocavirus	? 1 serotype
Others	Hantavirus, enterovirus, measles, chickenpox, cytomegalovirus

MERS Middle East respiratory syndrome, *SARS* severe acute respiratory syndrome

respiratory system and cause clinical and subclinical infections, but there is a certain preference of viruses for compromising specific levels of the respiratory system (Table 28.2). In this way, during an epidemic of a virus such as RSV or influenza, the major proportion of upper and lower respiratory tract infections will be caused by the prevalent virus. In addition, there will be an important incidence of subclinical infections, which act as efficient sources of transmission. As a result of herd immunity, important epidemics of multiple different viruses do not usually coexist in a community; instead, they alternate in terms of their presence in the community. For example, in Chile, the most commonly observed pattern involves parainfluenza outbreaks, followed by influenza outbreaks, and then RSV outbreaks; later, during winter–spring, metapneumovirus appears. Thus, the apexes of the epidemics follow one another and rarely overlap unless they affect populations of different ages. This phenomenon of viral interference may be explained by generation of interferon in infected patients, which “interferes” with the development of an infection of other viruses circulating at the same time.

These characteristics allow us to suspect specific causes of outbreaks or epidemics with reasonable certainty, considering associated clinical cases and detection of viruses at sentinel sites. Thus, a winter outbreak that involves infants under 1 year old and causes cases of obstructive bronchial illness will be due to RSV. A characteristic trait of influenza is an epidemic of disease that is marked by fever, cough, headache, and musculoskeletal aches, and that compromises preschool children, schoolchildren, and young adults. Parainfluenza virus outbreaks are associated with symptoms of hoarseness, gruffness, and cough, besides lower respiratory tract infections, in infants. Adenoviruses are feared because they sometimes cause intense feverish conditions and severe nosocomial infections.

Epidemiology contributes a lot to clarifying these situations, because alongside defining “suspicious cases” it implements diagnostic systems for circulating viruses (Fig. 28.1). The high infectivity of viruses makes epidemiological information vitally important in etiological clinical diagnosis, especially in terms of contact between sick patients and their relatives or close people in the community. The two kinds of respiratory virus that have the greatest impact on global health are RSV, which affects infants and elderly patients, and influenzas A and B, which compromise all of the population. Vaccines and

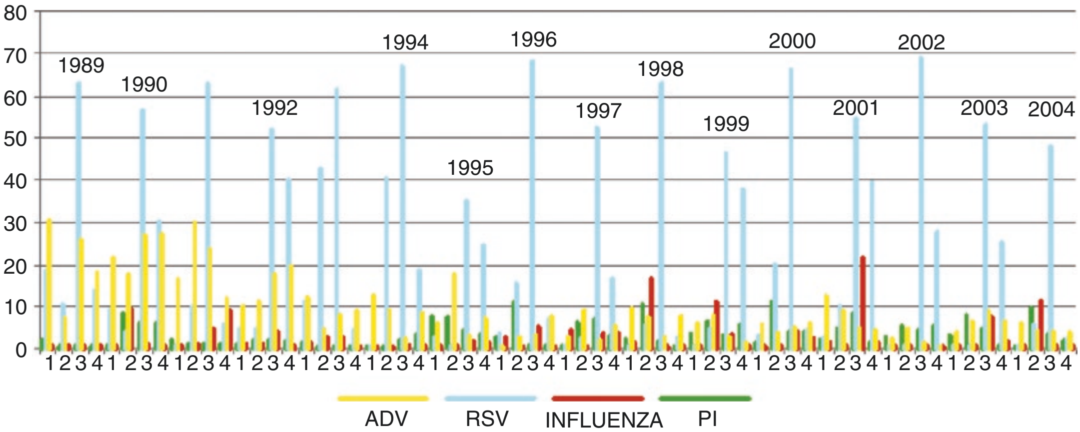

Fig. 28.1 Viral monitoring at Hospital Roberto del Río (Santiago, Chile). Detection of respiratory viruses (adenovirus, RSV, influenza, and parainfluenza) by immunofluorescence in infants hospitalized for acute lower respiratory tract infection in 1989–2004

antivirals have been developed just for influenza virus.

Viral respiratory infections are a very good example of a model of acute viral infection, in which viruses affect the individual, with or without symptoms, and then they leave him or her within a period of days or weeks. The course of infection depends on the interaction of various factors depending on: (1) the human host: age, immune status (based on previous infections and vaccinations), activity, tobacco use, etc.; (2) the virus: infecting dose, type, serotype, and viral strain; and (3) the environment: season, weather, humidity, contamination, geographical location, rural/urban setting, hospital/community, etc. From the host standpoint, acute respiratory infections are more frequent in childhood, particularly in infants and children under 2 years old, who represent the group with the biggest serious risk.

Diagnosis

Specific diagnosis of respiratory viruses is quite attainable nowadays because there are several immunodiagnostic techniques (immunofluorescence, enzyme-linked immunosorbent assay (ELISA), immunochromatography) available at public and private centers. They are easy to implement, with reasonably acceptable sensitivity and specificity, allowing appropriate study of cases that need it. Nowadays, molecular techniques (polymerase chain reaction (PCR) and reverse transcription PCR) are also available in many laboratories; they have high sensitivity and specificity, and provide results in less than 24 hours. The great sensitivity of these techniques enables detection of many agents, even in the same sample, raising questions about their interpretation. In severe cases or in deceased patients, they should always be implemented to establish the causes.

Emergent Infections

Among respiratory viruses, very good examples of "viral emergencies" are found, the most classic being the occurrence of global epidemics of influenza A virus derived from birds or pigs in 1918, 1957, 1968, and 2009; on these occasions, the virus broke through the species barrier and, thanks to multiple mutations, was able to transmit itself efficiently and establish itself as a "human virus." A pandemic of severe acute respiratory syndrome (SARS) due to a coronavirus is another example of a phenomenon that has threatened the world and was able to be controlled. During August 2014, an outbreak of lower respiratory tract infections in children, associated with enterovirus D68, started in the USA, and its evolution is ongoing. Likewise, an emergency involving the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) started in Saudi Arabia in 2012. Probably of animal origin (camels and bats) and transmissible through air, it has caused over 900 cases (30% lethal); luckily, it has not expanded efficiently in other territories.

Pathogeny of Viral Infections

Some viruses have certain particularities that require special consideration (Table 28.3). This process is described considering a population as a host. There are over 200 respiratory viruses capable of infecting humans, with diverse structures—RNA or DNA, naked or enveloped—and although they can be grouped into a few families, the great variety of serotypes, genotypes, and strains that can be identified entails the existence of many different potential pathogens.

The source of infection is usually another human carrier of the virus with or without an evident clinical infection. Even though viral shedding is greater in symptomatic cases, the relative isolation that viruses suffer when the host is resting in bed makes viral dissemination less efficient; in contrast, in slight or subclinical cases, despite eliminating smaller amounts of the virus in secretions, patients continue doing their normal activities, actively contributing to viral diffusion. In many respiratory infections, preschool children and schoolchildren are the main disseminators of the virus because they satisfy the following two conditions: shedding of high virus concentrations through secretions, and regular and close contact with their schoolmates and relatives.

Likewise, the chance of infection from animals exists, as in hantavirus cardiopulmonary syndrome, in which the source of the virus is a rodent. Emergence of influenza pandemics always represents a latent threat because they have origins in avian or swine viruses. These new strains have been able to adapt to the human host, converting him or her into a viral reservoir. Also, coronaviruses, which usually cause upper respiratory tract infections, have represented global threats because of the emergence of animal strains that have acquired the character of pandemics (e.g., SARS).

Table 28.3 Respiratory syndromes

Syndrome	Responsible virus[a]
Common cold	Rhinovirus ++++ Coronavirus ++
Pharyngitis	Adenovirus +++ Influenza virus ++ Parainfluenza virus ++
Laryngitis	Parainfluenza virus ++++ Influenza virus ++
Influenza	Influenza viruses A and B ++++ Parainfluenza viruses 1–3 ++ Hantavirus
Bronchiolitis	Respiratory syncytial virus ++++ Metapneumovirus +++ Parainfluenza virus ++
Pneumonia	Respiratory syncytial virus +++ Influenza virus ++ Metapneumovirus ++ Parainfluenza virus 3 ++ Adenovirus + SARS virus Hantavirus
Subclinical infection	Any of the viruses listed above

SARS severe acute respiratory syndrome
[a]The number of plus symbols listed for each virus denotes its relative degree of responsibility for the relevant syndrome

The infection mechanism works through respiratory secretions that are eliminated as big particles (>5 μm in size), which remain both on the hands and in the environment (on aprons, toys, medical instruments, and furniture), or small particles (<5 μm in size: Flügge droplets), which can form aerosols and stay suspended in the environment. A sneeze or a cough can expel secretions at 65 km/h over a distance of 9 meters. For some viruses, such as rhinovirus or RSV, contact with contaminated hands represents the main form of transmission.

The upper respiratory mucosa is the portal of entry (including the ocular conjunctiva for some viruses) and also represents the target organ of these viral infections. Dissemination within the organism happens because of the contiguity of the mucosa, contaminated secretions, or virus diffusion due to the proximity of infected cells and healthy cells. Even though the virus can escape into the blood and other territories, this phase of viremia is not essential to the pathogeny of the infection, and this is why respiratory virus are considered localized infections.

The following pathogenic facts explain five basic clinical and epidemiological concepts shared by respiratory viruses:

1. The incubation time is very short, from hours to 5 days.
2. There is abundant production of the virus at the portal of entry, which facilitates viral shedding and high infectivity.
3. Viral diffusion via mucosal proximity causes simultaneous and bilateral compromise of more than one segment of the respiratory airways and their annexes—for example, the paranasal sinuses and the middle ear.
4. The defense mechanisms in play—both innate and specifically acquired (immunoglobulin A)—are mainly of a local character.
5. Specific immunity is temporary and lasts only for some months (Table 28.4).

Table 28.4 Clinical and epidemiological consequences of the pathogeny of respiratory viral infections

Consequences
Transmission Directly from person to person Through big droplets (>5 μm in size) deposited in the environment (secretions on hands, clothes, furniture, toys) and small droplets (<5 μm in size) that form aerosols Potential animal sources of influenza virus (birds, pigs, and others) and hantavirus
Portal of entry = target organ Short incubation time, from hours to a few days High infection rate in the community
Localized infection = local defense mechanisms prevail Innate immunity: epithelial barrier (cilia, coughing, associated lymphatic tissue) and inflammatory response (leukocytes, macrophages, fever, cytokines) Acquired immunity: local (immunoglobulin A) and general (immunoglobulin G), T lymphocytes CD8–CD4 (type 1 and type 2 helper T cells); short-duration immunity with frequent reinfections
Propagation by proximity In individuals, it simultaneously compromises many levels of the respiratory system in a bilateral way In the community, it affects various members with close contact within the family, at school, or at work; it is hard to contain with isolation measures or physical barriers

Prevention of viral respiratory infections is difficult because high infectivity is favored by the presence of subclinical infections, human sociability, and unavailability of vaccines, except for influenza virus vaccines. Treatment is fundamentally symptomatic and essentially consists of maintenance of the permeable airway, oxygen administration, and assisted mechanical ventilation in extreme cases. Use of antiallergics, anti-inflammatories, steroids, bronchodilators, and prophylactic antibiotics is very controversial, and this is discussed in other chapters in this book. Antivirals are available just for influenza viruses and, if they are administrated early, they shorten the symptomatic period but seemingly do not prevent development of serious illness in high-risk patients.

Epidemiological Management: The Winter Plan

In countries with temperate weather, the incidence of acute respiratory infections increases in cold seasons because of the appearance of viral epidemics. RSV is the virus most responsible for this and usually coincides with influenza outbreaks. In addition, respiratory adenoviruses appear endemically, with unpredictable increases that can acquire relevance because of their clinical seriousness and propensity to cause inpatient infections at times of overload in hospitals. Despite prevention not being efficient and the fact that there is no specific treatment for respiratory viruses, health care (both public and private) can be organized for prevention of severe cases and deaths.

RSV appears "all winter" and its outbreak lasts for 3–5 months. It has been estimated that 60% of children who are born are infected during the first year of life, and all children have had contact with it by their second year; 25–40% of primary infections evolve as acute lower respiratory tract infections, and 2% of them require hospitalization. Influenza viruses usually appear in autumn in epidemics that last for 6–8 weeks. Accordingly, the demand for pediatric care increases during every winter; the emergence of RSV dominates bed availability for infants in hospitals and increases the need for ambulatory care, while influenza viruses dominate consultations for preschool children, schoolchildren, and adults.

This increase in the demand for pediatric ambulatory and hospital care forces us to adopt special measures for management of acute lower respiratory tract infections—the most serious pathology. They have to be implemented at both the ambulatory and hospital levels. The objective of this "winter campaign" is to prevent deaths from acute lower respiratory tract infections, and it should be directed preferentially toward those children and adults who are at greater risk of developing severe illness.

At the ambulatory level, the campaign should be focused on two aspects:

- Education of the population for recognition of serious symptoms (long-lasting fever, respiratory distress, wheezes, apnea, etc.) to encourage early medical consultation, particularly in higher-risk populations such as preterm infants, chronic disease patients, immunosuppressed patients, and, in general, patients under 3 months of age.
- Increased pediatric ambulatory care, including prolongation of clinic hours (afternoons, nights) for pediatric and kinesiotherapy care, increased availability of bronchodilators (salbutamol) and antimicrobial medication (amoxicillin), and implementation of ambulatory oximetry and oxygen therapy.

At the hospital level, the following measures are recommended:

- Anti-influenza and antipneumococcal vaccination.
- Local implementation of rapid diagnosis of RSV, influenza, and adenovirus (using immunofluorescence or ELISA).
- Reinforcement of medical and paramedical at emergency medical clinics and in hospital emergency rooms and intensive care units. For this purpose, operating rooms are "repurposed" and realigned for attention to respiratory cases, with equipment for administration of oxygen. Institutional conventions are also established for facilitating transfer of severely ill patients.
- Ensuring the availability of cubicles for isolation of individual patients (for admissions and for cases of suspected or confirmed adenovirus).

In Chile, these measures have been applied every year since 1990, with great success in reducing deaths, though morbidity has not decreased, because that depends on the development of vaccines of high effectiveness (Fig. 28.2).

Epidemiology of the Most Frequent Bacterial Infections

Unlike respiratory infections with a viral cause, infections of bacterial origin, while frequent, affect a smaller group of the population, given their characteristics in terms of pathogenicity, transmissibility, and preventive measures such as use of specific vaccines.

In the following sections, we discuss the epidemiology of respiratory infections caused by *Streptococcus pneumoniae* and *Bordetella pertussis*.

Streptococcus pneumoniae

Pneumococcus is the main cause of bacterial pneumonia in all age groups across the globe. Its incidence varies according to the age group, the development status of the country, and employment of specific vaccines. It is now by far the most frequent causal agent of pneumonia since the incidence of pneumonia caused by *Haemophilus influenza* type B was reduced by introduction of a specific vaccine, which practically made infections with that causal agent disappear. The most relevant risk groups are infants <2 years old, adults over 60 years old, and immunosuppressed patients. The WHO estimates that this agent causes the deaths of 700,000 to one million people every year.

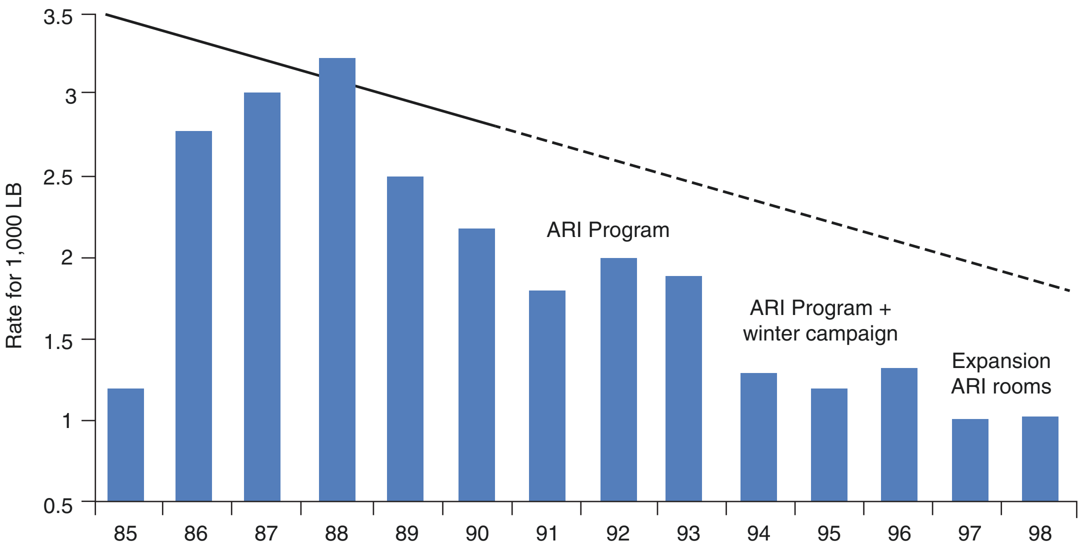

Fig. 28.2 Infant mortality due to pneumonia in Chile, 1985–1998 (Rev Chil Pediatr (2001))

In Chile, we know, with reasonable accuracy, the epidemiology of invasive pneumococcal infections (meningitis, septicemia, bacteremia), since they are under laboratory monitoring. Nevertheless, the great majority of pneumococcal pneumonias are not bacteremic, which is why the incidence of pneumococcal pneumonia is unknown; there are just data extrapolated from monitoring of pneumonia in hospitalized patients, assuming that pneumococcus is the primary cause of bacterial pneumonia at any age.

Before universal vaccination with a pneumococcal conjugate vaccine was introduced, the incidence of this disease in Latin America was between 61/100,000 in patients under 2 years old and 32/100,000 in patients under 5 years old, subsequently decreasing with age.

In Chile, vaccination with a 10-valent pneumococcal conjugate vaccine was introduced in 2011 for children born since November 2010. Between 2011 and 2014 the rate of invasive infections in patients under 2 years old decreased from approximately 39/100,000 to 8.7/100,000, although there has been no impact of vaccination in other age groups; on the contrary, an increase in cases has been seen among patients over 65 years old (Fig. 28.3).

The most prevalent serotypes prior to the use of vaccines were 5, 14, and 1. In the last postvaccination period they were serotypes 15, 1, and 7F, followed by serotypes 3, 19A, 6A, and 6B, although there were reductions in serotypes 15, 1, 5, and 6B. Since the introduction of vaccines, the proportions of serotypes 3, 19A, and 6A have increased in all age groups; those serotypes are not contained in the 10-valent vaccine but are included in the 13-valent one.

Susceptibility to penicillin in pneumococcal infection is an emergent topic that greatly worries clinicians, although management of pneumonias is not as important as management of pneumococcal meningitis. Since changes in the cut-off points in the definition of resistance to infections outside the central nervous system, susceptibility to penicillin has remained low. Resistance to penicillin is greater in patients under 5 years old than in other age groups, which is why this topic is more relevant to pediatric populations.

The most recent report of the Chilean Public Health Institute showed that the rates of intermediate sensitivity to penicillin and cefotaxime were 1–3% in the preceding 2 years, and the rate of resistance was 0%. When analyzed by age group, it was observed that for patients under 5 years old, the rate of intermediate sensitivity was 4% for penicillin and 5% for cefotaxime between 2007 and 2014, with a 0% rate of resis-

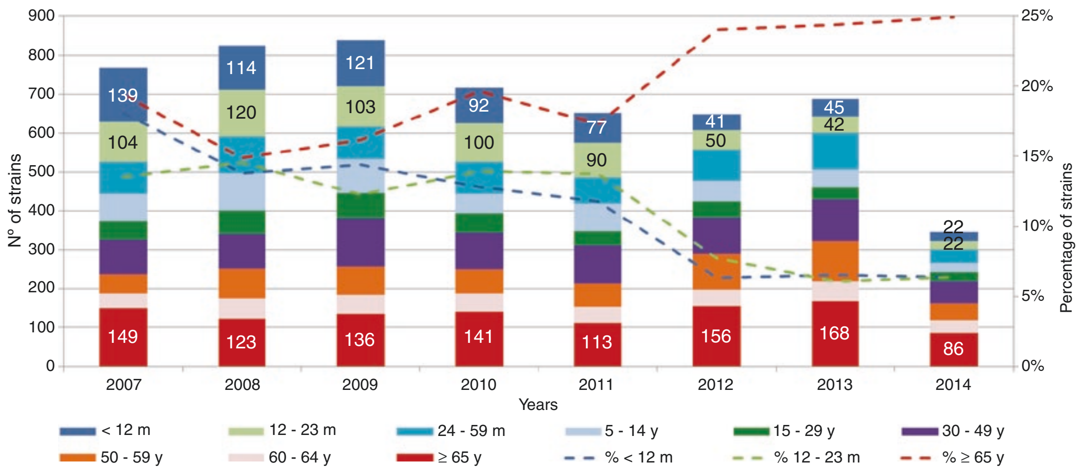

Fig. 28.3 Confirmed cases of invasive pneumococcal disease in Chile

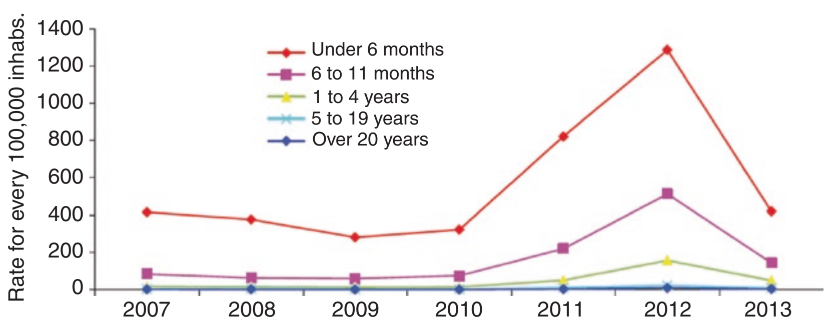

Fig. 28.4 Incidence of whooping cough in Chile

tance to these antibiotics. The rate of resistance to macrolides in the same age group reached 47%, while the rate of susceptibility to levofloxacin and vancomycin remained at 100%.

Bordetella pertussis

B. pertussis is a causal agent of respiratory infections that pose a serious risk of mortality in young infants, especially those under 6 months old. Thanks to the introduction of vaccines in the 1950s and 1960s, the incidence and mortality rates have decreased significantly. However, despite the high coverage rates for the vaccine, and although humans are the only reservoir for *B. pertussis*, control and elimination of its circulation have not yet been accomplished.

Its distribution is ubiquitous, with over 50 million cases and 300,000 deaths annually. The majority of the mortality is concentrated in patients under 1 year old, particularly in those under 6 months old.

In Chile, during the early 1990s, a sustained increase in the incidence started to be registered, starting from less than 4/100,000 and reaching 25/100,000 between 1996 and 2000. After 2010 and 2012, a new increase in cases, with incidence rates of up to 35/100,000, was observed.

Incidence rates vary according to the age group, reaching the highest rate (136/100,000) in infants under 12 months old and then dropping to 19/100,000 in children between 1 and 4 years old (Fig. 28.4). Cases in patients under 1 year old represent 42% of all notified cases and, of those, 82% are under 6 months old.

A feature shared by all of these epidemic outbreaks is that mortality is concentrated in young infants, who are not protected by the primary scheme of three vaccine doses, which is not completed until the child is 6 months of age.

Several studies on the source of infection of *B. pertussis* in young infants have shown that the main sources are intrafamily contacts. The vaccine loses its effectiveness 5 to 7 years after the vaccination is completed, which is why adolescents and adults can be infected.

Since whooping cough does not always manifest as classic clinical cases in adolescents and adults but, rather, is characterized by a persistent cough, suspicion levels are low and appropriate diagnosis is often not made; thus, there is no timely treatment. This situation facilitates infection of infants within a family group.

On the basis of this epidemiology, between 2011 and 2012 the Capullo control program took place in Chile, in which the entire family groups of newborns and vaccination of adolescents in the eighth grade was performed. In 2013 the incidence dropped to less than 12/100,000, and in 2014 the aggregated incidence reached 4.6/100,000.

These numbers show us that whooping cough is a disease that affects all age groups, but its biggest impact in terms of both morbidity and mortality is in patients under 6 months old.

Multiple strategies have been tested internationally, but none of them have been very effective. A combination of different strategies seems to be the key, such as systematic and permanent vaccination in pregnant women, adolescents, and family groups. Creation of a vaccine with proven high efficacy in controlling this disease in the short term has not yet been accomplished.

Clinical suspicion is very important for appropriate treatment of cases, in both adults and infants, to reduce the risk of transmission in the former and to reduce mortality in the latter.

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