ESTIMATED IMPACT OF DIFFERENT VARICELLA VACCINATION STRATEGIES IN VALENCIA, SPAIN

Impacto estimado de diferentes estrategias de vacunación de Varicela en Valencia, España

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ABBREVIATIONS

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- ACIP: Us advisory committee on immunization practices
- CDC: Center of Disease Control
- CMBD: National immunization Basic Data set
- CMI: Cell Mediated Immunity
- DNA: Deoxyribonucleic Acid
- FDA: Food and Drug Agency
- GP: Glycoprotein
- GPFC: Guinea Pig Fibroblast Cells
- GPS: Global Positioning System
- HELF: Human Embryo Lung Fibroblasts
- HSV: Herpes Simplex Virus
- HZ: Herpes Zoster
- IgG: Immunoglobulin G
- MCCV: Meningococcal C Conjugated Vaccine
- MMRV: Measles Mumps Rubella Vaccine
- NASA: National Aeronautics and Space Administration
- NIAID: National Institute of Allergy and Infectious Diseases
- NIH: National Institute of Health
- ORFs: Open Reading Frames
- OTC medications: Over-the-counter drugs
- PCR: Protein Chain Reaction
- PHN: Post herpetic Neuralgia
- PVL: Precio venta al laboratorio
- UK: United Kingdom
- US: United States of America
- VAERS: Vaccine Adverse Event Reporting System
- VHS-1: Virus Herpes Simplex 1
- VHS-2: Virus Herpes Simplex 2
- VZV: Varicella zoster Virus

RESUMEN (SUMMARY)

1. RESUMEN (SUMMARY)

1.1. INTRODUCCIÓN

La vacuna de la varicela es eficaz y segura, a pesar de ello, muchos de los países desarrollados no la utilizan de manera habitual. Entre los motivos se encuentran que la enfermedad es considerada una patología benigna que habitualmente ocurre en niños, que la vacuna puede hacer que la enfermedad se desplace a edades superiores, donde es más severa, y un potencial aumento de la incidencia de herpes zoster en personas no vacunadas. Más de 30 años después de la autorización de la vacuna, la discusión continúa.

Cuando este proyecto comenzó, la Agencia Española del Medicamento había bloqueado la distribución de la vacuna de la varicela basándose en la hipótesis de que coberturas vacunales parciales como las obtenidas en España, entre un 50 y 60%, podría tener efectos epidemiológicos negativos, como el aumento de los casos en adultos. Otras causas serían el desconocimiento acerca de la duración de la inmunidad, que podría disminuir con el tiempo, y el tercer punto es la relación controvertida de la vacuna de la varicela y del aumento de herpes zoster.

Por estos motivos, decidimos modelar el impacto de la vacunación parcial de varicela sobre la epidemiología de la enfermedad, sin tener en cuenta lo que ocurriría con el herpes zoster en el futuro, puesto que la relación no es clara todavía.

Por otro lado, en países desarrollados, el coste-efectividad de la vacuna debe ser evaluado, puesto que se requiere para la implementación de cualquier programa de vacunación. Muchos estudios han demostrado que la vacuna de la varicela es coste-efectiva desde el punto de vista de la sociedad, pero no todos han demostrado que también lo es para los organismos que pagan las vacunas, por lo que decidimos realizar también un estudio económico de las distintas estrategias de vacunación de la varicela.

La finalidad de este estudio es estimar la epidemiología de la varicela con diferentes estrategias de vacunación y coberturas vacunales, para poder aconsejar a los

encargados de las tomas de decisiones acerca de si la vacuna de la varicela debería ser administrada, cuando y donde debe ser administrada y quien debe pagar por estas dosis.

El modelo utilizado es una herramienta útil para proponer y comparar diferentes situaciones respecto a la enfermedad, se puede modelar la epidemiología futura a largo plazo con cualquier calendario vacunal. Además, puede ser modificada para simular otras enfermedades cambiando parámetros como: infectividad, variación semanal, distribución por grupos de edad, etc.

1.2. HIPÓTESIS Y OBJETIVOS

1.2.1. HIPÓTESIS

Cuando comenzó este proyecto, la vacunación de la varicela no era universal, y las coberturas vacunales eran bajas. Nuestras hipótesis son:

- La vacunación no sistemática de la varicela en la Comunidad Valenciana disminuye el número de casos de varicela sin un aumento del número de casos en adultos.
- La vacunación universal de la varicela es coste-beneficiosa en la Comunidad Valenciana.

1.2.2. OBJETIVO PRINCIPAL

- Estimar el impacto de las diferentes estrategias de vacunación en la Comunidad Valenciana:
    - Vacunación universal del niño al año y a los 3 años,
    - Vacunación de los grupos de riesgo y del preadolescente,
    - Vacunación individual no sistemática en los niños.

1.2.3. OBJETIVOS SECUNDARIOS

- Evaluar el impacto de la vacunación de la varicela con cobertura vacunal parcial en la incidencia de varicela en adultos.

- Calcular el efecto coste-beneficio de la estrategia de vacunación universal en la Comunidad Valenciana.
- Calcular el efecto coste-beneficio de la estrategia de vacunación de los grupos de riesgo y del preadolescente en la Comunidad Valenciana.
- Calcular el efecto coste-beneficio de la estrategia de vacunación no sistemática y del preadolescente en la Comunidad Valenciana.

1.3. MATERIALES Y MÉTODOS

El riesgo de adquirir varicela en la vida es mayor del 95%, ocurriendo aproximadamente en el 90% de los casos en niños menores de 10 años. Se cree que la incidencia de varicela varía cada semana del año, por lo que incluimos esta variabilidad y el riesgo de adquirirla en nuestro estudio.

Respecto a la vacuna de la varicela, tiene una efectividad elevada, aunque estos resultados varían dependiendo de la población de estudio y de la metodología del mismo. Se ha demostrado que una vacunación con dos dosis es más efectiva que una vacunación con una única dosis. Para ir en contra de la vacuna y disminuir las críticas hacia el estudio, decidimos realizar un estudio de sensibilidad con una pérdida de efectividad de la vacuna de un 1% al año comenzando 15 años después de la administración de la vacuna.

El análisis económico de la vacunación de la varicela se realizó incluyendo datos económicos en el modelo dinámico, incluyendo coste de la vacuna, de la manipulación de la misma, de la cadena de frío, administración, etc. También se tuvieron en cuenta gastos indirectos, como coste de consulta médica, de urgencias, de hospitalización y de pérdida laboral, entre otros.

Para el estudio, realizamos un modelo matemático de ecuaciones diferenciales. El modelo básico era: Susceptible-Latente-Infectado-Recuperado, con dos estados intermedios de latencia. Se organizaron los grupos de edad atendiendo a la vacunación y gravedad de la enfermedad:

- 0-6 meses de edad
- 6-12 meses
- 1-3 años
- 3-12 años
- Mayor de 12 años

La estructura del modelo era la observada en la Figura A.

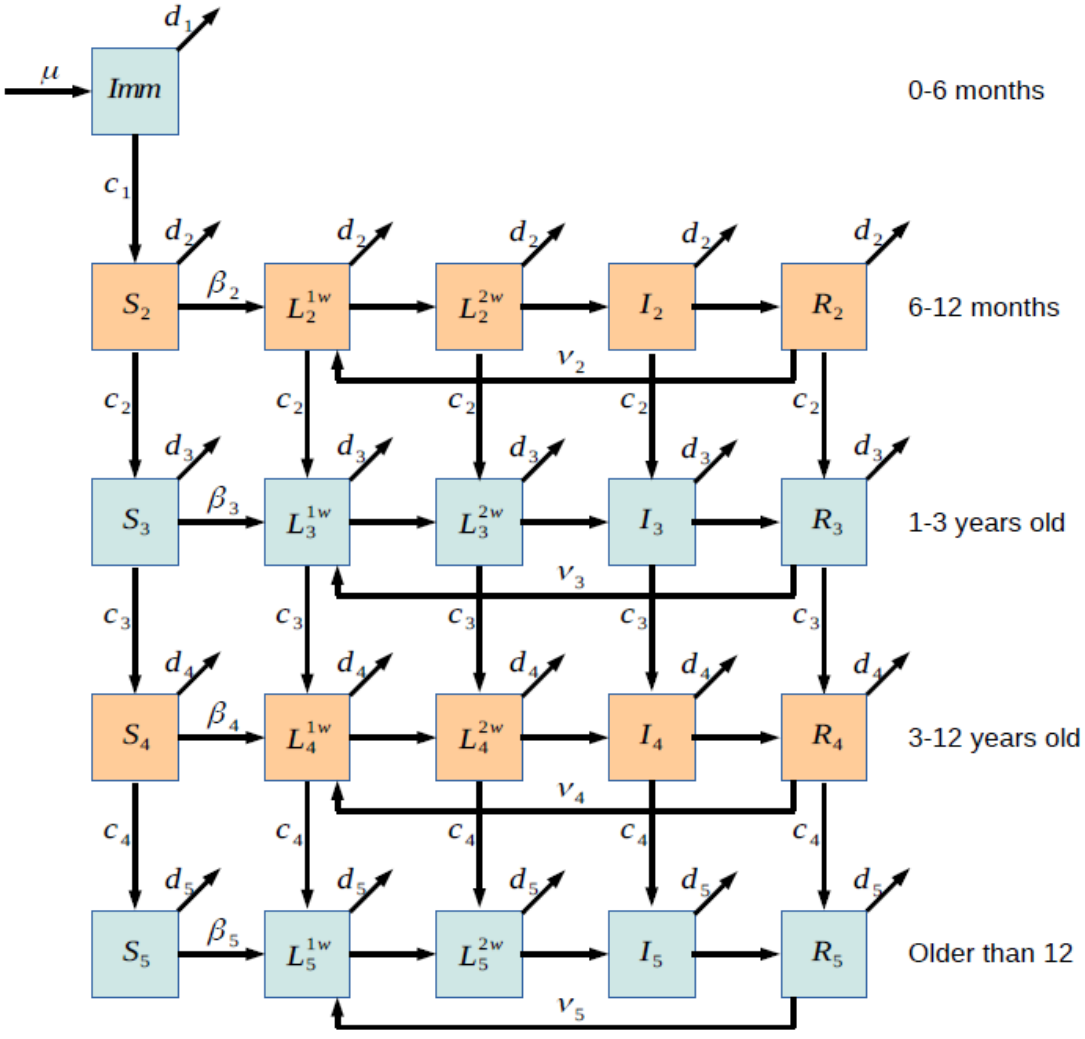

Figura A. Modelo compartimental por grupos de edad de la varicela.

Durante los 6 primeros meses de vida, se considera al niño inmune por transmisión de los anticuerpos maternos. La transmisión de la enfermedad a partir de ese momento es variable por grupo de edad y por semana del año.

Las diferentes estrategias de vacunación analizadas fueron las siguientes, simulando 50 años desde el inicio de la vacunación:

1. Caso base: no hay vacunación.
2. Vacunación a los 12 años: vacunación de los niños en grupos de riesgo y del preadolescente que alcanza los 12 años sin historia de vacunación ni de haber padecido la varicela. Este era el programa en la Comunidad Valenciana cuando el estudio se inició.
3. Vacunación universal: vacunación con 2 dosis, a los 12 meses y a los 3 años de edad, con una cobertura vacunal del 96%. Los niños que alcancen los 12 años sin vacunación ni historia de enfermedad son vacunados con una cobertura del 90%. El sistema sanitario paga los costes de la vacuna. Este es el calendario actual en la Comunidad Valenciana.
4. Vacunación individual: además del programa de vacunación a los 12 años, los padres pueden comprar la vacuna para ser administrada a los niños de 1 y 3 años, con coberturas variables del 10-90%. Esta era la situación en la Comunidad Valenciana antes de 2014, cuando se retiró del mercado.

1.4. RESULTADOS

El modelo fue calibrado y ajustado para reproducir el número de infecciones semanales, replicado durante 4 años. La tasa de infección es desconocida, pero se estimó para cada semana del año, teniendo así un modelo muy similar a los datos disponibles de estudios previos. También se calibró el modelo para los diferentes grupos de edad estudiados.

1.4.1. Impacto de las diferentes estrategias de vacunación en la epidemiología de la varicela.

Con la vacunación a los 12 años exclusivamente, hay una pequeña disminución del número de casos, que representan los casos de varicela en adultos. En el momento en el que comienza la vacunación en el niño, hay un descenso importante del número total de casos, directamente proporcional a la cobertura vacunal, desapareciendo casi por

completo la enfermedad cuando se alcanzan coberturas del 90%, debido a la inmunidad de grupo.

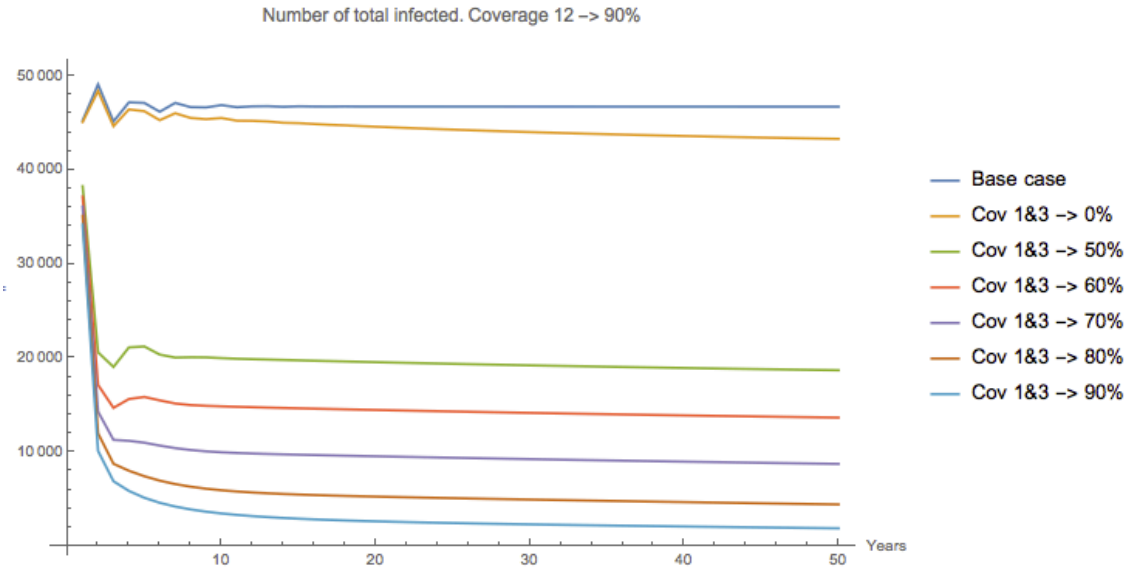

Figura B. Número total de individuos infectados por año en los próximos 50 años, con diferentes coberturas vacunales.

La enfermedad es considerada más severa en adultos, y uno de los motivos por los que se retiró la vacuna es porque se pensaba que la enfermedad se iba a trasladar a edades superiores.

El modelo predice un descenso del número de infectados mayores de 12 años con cualquier cobertura vacunal.

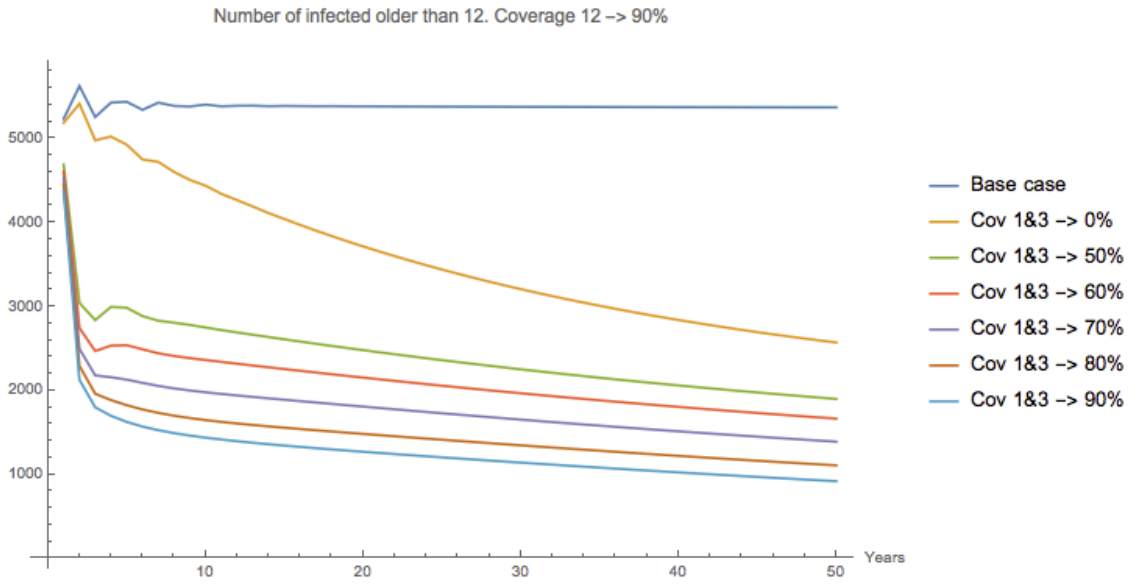

Figura C. Número de individuos mayores de 12 años infectados por año durante los próximos 50 años, con diferentes coberturas vacunales.

Se realizó un análisis de sensibilidad asumiendo una pérdida de inmunidad de 1% por año a partir de 15 años tras la administración de la pauta de vacunación completa con 2 dosis. Incluso en este caso, se observa una disminución importante en el número de casos de varicela comparado con el caso base.

El número estimado de sujetos infectados mayores de 12 años también disminuye. Es a estas edades donde se observa un mayor efecto tras esta pérdida de inmunidad, pero a pesar de ello hay una disminución del número de casos comparado con el caso base.

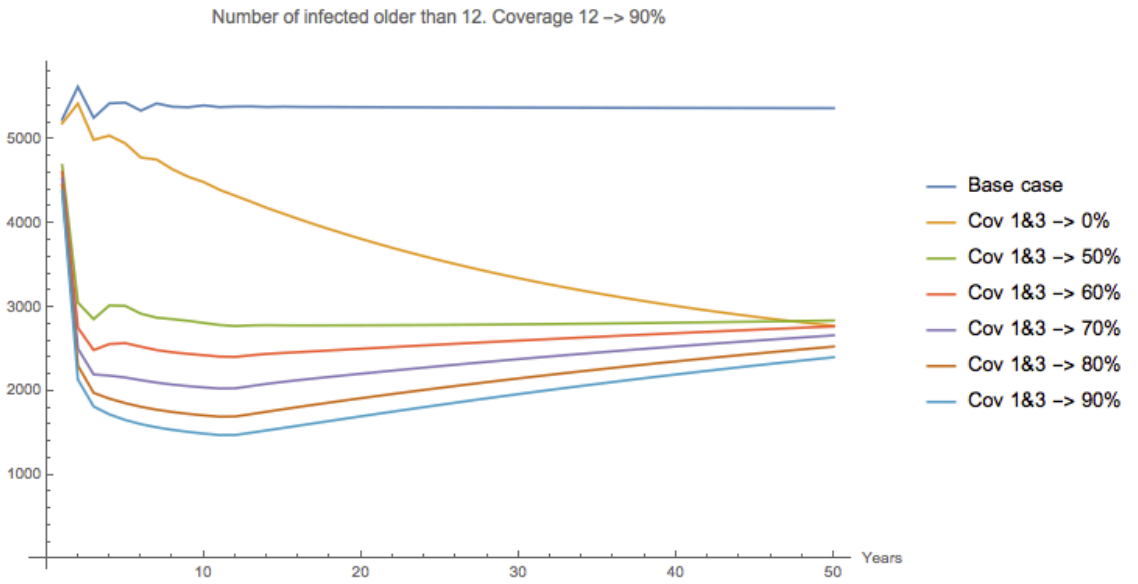

Figura D. Número de individuos mayores de 12 años infectados por año, con diferentes estrategias de vacunación, asumiendo una pérdida de inmunidad de un 1% al año comenzando 15 años tras la administración de la segunda dosis de vacuna de la varicela.

1.4.2. Transición de vacunación parcial a vacunación universal

Durante el desarrollo de la tesis, el calendario de vacunación en España cambió a universal, por lo que tuvimos que adaptar el modelo para mostrar el impacto de este cambio. Consideramos que tras vacunación parcial se cambiaba el calendario a vacunación al año y los 3 años, manteniéndose el catch-up a los 12 años. Consideramos de inicio una cobertura del 50% en niños y del 90% en preadolescentes y 25 años tras el inicio de la vacunación, la estrategia vacunal se mantenía únicamente en los niños, alcanzando una cobertura del 95%.

Con esta nueva estrategia consideramos 3 posibles escenarios:

1. Cuando comienza la vacunación universal se retira la vacuna a los 12 años.
2. Cuando comienza la vacunación universal, se mantiene la vacuna en el preadolescente 11 años, hasta que el primer niño no vacunado cumple 12, y posteriormente se retira la vacuna a los 12 años.
3. Se mantiene para siempre la vacunación a los 12 años.

La diferencia entre el número total de infectados entre el escenario 1 y el 2 y entre el escenario 1 y el 3 se puede ver en la Figura E:

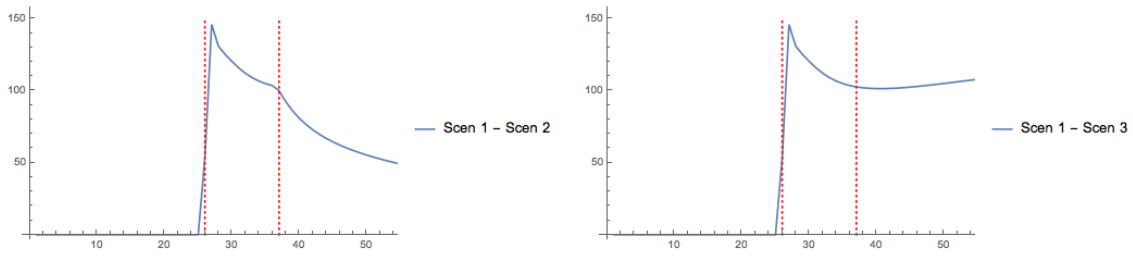

Figura E. Número de casos de varicela comparados con retirada de la vacunación a los 12 años cuando comienza la vacunación universal. A) Vacunación a los 12 años se mantiene durante 11 años tras el inicio de vacunación universal. B) Vacunación a los 12 años se mantiene para siempre.

El pico más elevado en ambas gráficas corresponde con el cambio de estrategia vacunal y la introducción de la vacunación universal. En la gráfica A podemos observar que al inicio de la vacunación universal la diferencia es de 150 casos en adultos por año, y tras 11 años, cuando se retira la vacuna del preadolescente, la diferencia disminuye a 50 casos en adultos, pero el cualquier caso hay una diferencia. Esto quiere decir, que el catch up ayuda a mantener una incidencia de infecciones, especialmente en adultos. En la gráfica B, la diferencia de 150 casos en adultos se mantiene en el tiempo, puesto que se mantiene la vacunación en el preadolescente. Por lo tanto, si se retira la vacunación a los 12 años cuando comienza la vacunación universal, va a haber un mayor número de individuos infectados que si se mantiene 11 años y para siempre.

1.4.3. Resultados farmacoeconómicos

Los costes de la vacuna de la varicela, incluyendo costes directos e indirectos, ascienden a aproximadamente 12.822.330€ por año. Con cualquier programa de vacunación se ahorran costes.

Con el programa de vacunación donde el sistema sanitario paga únicamente las vacunas a los 12 años y grupos de riesgo y las vacunas no están disponibles para su compra, el coste de la varicela desciende aproximadamente 1,3 millones de euros al año, principalmente debido al descenso de los costes indirectos.

Sin embargo, con el programa de vacunación universal, donde el sistema sanitario paga las vacunas de los niños y preadolescentes, los ahorros totales etsarían casi en 8 millones de euros al año.

Del mismo modo, la vacunación al año y 3 años pagada por los padres también produce un descenso en el coste total de la varicela, no importa qué cobertura vacunal se alcance. A medida que aumenta la cobertura vacunal en el niño, los ahorros para el sistema sanitario son mayores, puesto que pagan menos vacunas para los niños de 12 años y el número de adultos y niños infectados desciende, disminuyendo así los costes directos e indirectos de los mismos.

1.5.CONCLUSIONES

- El número total de casos de varicela disminuye cuando se administra un catch up a los 12 años, sin importar la cobertura vacunal al año y a los 3 años.
- El número total de infectados mayores de 12 años no se modifica con la administración de la vacuna de la varicela a niños, sin importar la cobertura vacunal de estos. Por tanto, hay un descenso en el número total de casos sin traslado de la enfermedad a edades superiores.
- Incluso si hay una pérdida de inmunidad del 1% al año comenzando 15 años tras la administración de la vacuna, el número total de casos tras la vacunación será siempre menor que el número de casos sin ella.
- Se observa una importante inmunidad de grupo cuando las coberturas vacunales al año y 3 años son mayores del 70%. Por debajo de esta, se mantiene el efecto de la vacunación con una disminución directamente proporcional a los vacunados.
- El número de individuos e 12 años es mayor que en el caso base, pero cuando alcanza coberturas de 70% comienza a disminuir debido a la inmunidad de grupo, y cuando supera el 80%, el número de individuos que alcanza los 12 años siendo susceptibles es mucho menor que en el caso base.
- Hay un aumento de vacunación a los 12 años cuando hay coberturas vacunales bajas en los niños.
- Es esencial que el programa de vacunación catch up se mantenga hasta que los niños alcancen coberturas vacunales por encima del 90%.
- La vacunación universal con dos dosis ahorra recursos económicos de aproximadamente 8 millones de euros al año al sistema sanitario, ahorrando también a la sociedad general.

INTRODUCTION

2. INTRODUCTION

Varicella vaccine is highly efficacious and safe, however there are many developed countries that do not use it regularly. Among the reasons are that chickenpox is considered a benign infection in children, that the vaccine may shift the disease to older ages, when the disease is severe, and a potential increase of herpes zoster in the unvaccinated. More than 30 years after its licensure the discussion continues.

Varicella zoster virus (VZV) is responsible for varicella, commonly known as chickenpox, and herpes zoster, commonly referred to as shingles. Varicella results from primary infection with VZV. After this infection, the virus can remain latent in dorsal root ganglia and it can reactivate causing herpes zoster (1).

Back in 1767, Heberden established the clinical difference between varicella and smallpox. Von Bokay first described the relationship between varicella and herpes zoster in 1892, before the virus was discovered. In 1921, Lipschutz demonstrated that the lesions were histologically identical. Burnet and Buddingh proved the infection went from acute to chronic in 1950, and finally T.H. Weller, who later received the Medicine Nobel Prize, discovered the virus in 1952, when he first isolated the virus from a patient with chickenpox (2).

Takahashi initially thought Varicella and Zoster virus were two different viruses, but he run a clinical trial with immunocompromised children comparing the virus when they had clinical varicella and zoster, and noticed it was the same virus. In 1974, Takahashi produced a live VZV vaccine.

2.1. VARICELLA ZOSTER VIRUS

VZV is included in the herpes virus family, it is also known as Herpes virus 3.

There are eight human herpes viruses classified into three herpes virus subfamilies, Varicellovirus belongs to the alpha-herpesvirus family, which also includes Simplexvirus: Herpes simplex 1 and 2 (VHS-1 and VHS-2). There are two other subfamilies: beta- and gamma- herpesvirus.

Alpha-herpesvirus subfamily is the most aggressive of the Herpesviridae (2), due to its replication and infection properties. It is characteristic their latency period and their ability to destroy infected cells. They affect nervous cells, while other subfamilies usually infect blood cells.

Clinically, VZV is much more contagious than herpes simplex virus, has preference for the nervous system, and it affects more tissues and more aggressively. VZV has been related with dorsal ganglia and local nerves, and in autopsies the VZV DNA has been found in ganglia. These ganglia can be necrotic if a reactivation occurred during lifetime. When the virus reactivates, mainly affects the nervous system, but it has also been demonstrated that the virus can disseminate producing a viremia and other clinical symptoms rather than the characteristic herpes zoster rash.

There are five different genotypes of VZV distributed by geographic areas. During childhood there might be a coinfection of more than one genotype, which can give place to a new viral genetic recombination.

Virons are similar to other herpes virus, spherical with a diameter of 150-200 nm, and are composed of four structural elements: the envelope, the tegument, the nucleocapsid, and the core. They have a lipid envelope that encloses a 100nm capsid containing 162 capsomeres arranged in an icosahedral form (3).

The lipid envelope comes from the cell that has been infected and is composed by a double stranded lipid coat where VZV-specific glycoprotein spikes are found around all its surface (4). These are important for the transmission of the virus to non infected cells,

and induce the body immune response. If the disease is transmitted to a family member, it is much more severe than if it is transmitted to a non-genetically related person. Genes that form the lipid envelope that come from the infected cell can be shared by family members, so the virus with the envelope is recognized as its own and the virus will acquire the capability of being more aggressive in the following family members infected.

The capsid includes the genoma, and together form the nucleocapsid. The tegument is found between the nucleocapsid and the lipid envelope; it is distributed asymmetrically and includes proteins that are involved in the process of virus reproduction inside an infected cell, due to the transcriptional regulators found in it. They also may be involved in the capacity of the virus to have a latency stage and to be able to replicate in the ganglia and satellite cells. The tegument has a thickness of approximately 40 to 50 nm (3).

The nucleocapsid is composed of 162 capsomers and displays an icosahedral and axial symmetry. Finally, the core, inside of the nucleocapsid, contains one copy of the VZV double stranded linear DNA genome.

The genome is the smallest of all herpes virus: 125,000 base pairs, 70 open reading frames (ORFs), and its DNA is single gene, linear and double stranded, containing 69 single genes with little genetic variations (3).

The VZV particle is fragile, and its lipidic structure makes it susceptible to alcohol or other disinfectants, this is why the main source are human beings.

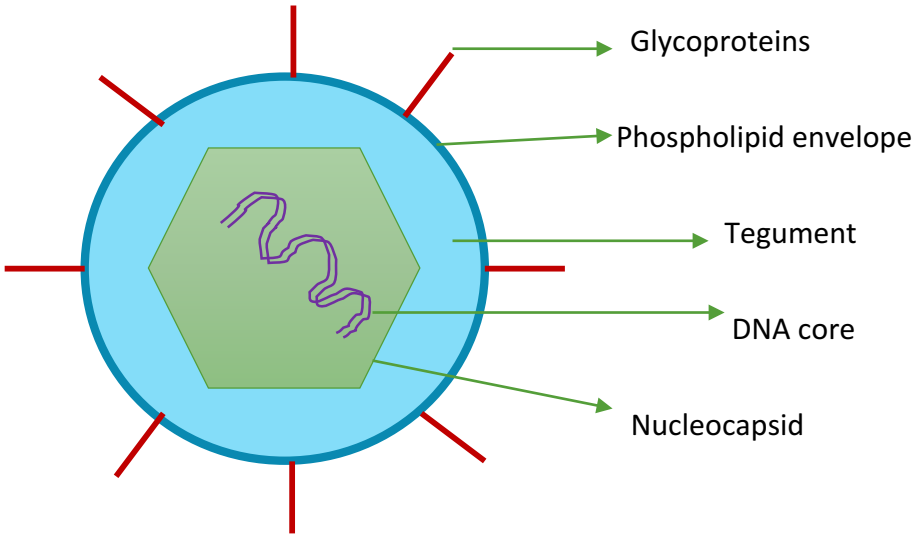

Figure 1. The morphology of Varicella Zoster virus. Modified from Harper et al. 1998 (3).

2.1.1. Glycoproteins.

There are currently eight known VZV associated glycoproteins: gE, gB, gH, gI, gC, gL, gK, and gM (5). They correspond with known glypcoproteins of herpes simplex virus, however, there is no equivalent of the major gp of HSV, gD, in VZV (6).

Glycoprotein E (gE), is present in many stages of maturation and it is necessary for VZV replication. It can serve as a cell surface receptor for immunoglobulin G. Glycoprotein B (gB) is involved in the entry of VZV into host cells. Glycoprotein H (gH) is required for growth in cell culture and host entry, egress, and cell-to-cell spread. Glycoprotein I (gI) is not essential for replication, but it may be important for cell-to-cell spread of the virus. Glycoprotein C (gC) is involved in the attachment to host cells. Glycoprotein L (gL) acts as a chaperone to gH, helping in its maturation, folding and transport to the cell surface.

The major gp, gE, is the most abundantly expressed and is highly immunogenic. It is linked to gI and with gI is a Fc receptor on infected cells (7). gE provides sequences that mediate assembly of viral proteins and envelopment in the trans-golgi network (8). gE and gI function as navigation GPS, directing others to the cell surface and trans-golgi

network, where final envelopment of virions takes place. The interaction between mannose 6-phosphate receptors and VZV GPS are important for viral entry and exit from cells.

2.1.2. Genetics.

The VZV genome is probably the smallest of all the herpesviruses, containing between 124,000 and 126,000 base pairs and with a G + C content of 46.02% (3). The DNA is used efficiently: it is estimated to encode between 70 and 150 proteins within 69 open reading frames (ORFs) and with few non-coding regions (9).

2.2. VARICELLA. PRIMARY INFECTION.

The Varicella Zoster Virus primary infection produces varicella. VZV is transmitted from person to person through virons present in vesicular fluid of skin lesions, and it is very contagious. The virus enters through the respiratory tract or conjunctiva (2). The transmission is not respiratory, although the virions can be present on lesions of the palate. It is believed that it can replicate at the site of entry, the nasopharynx or in regional lymph nodes. The patient is contagious from a few days prior to the disease manifestations until the vesicles disappear. It is believed that it is contagious only 24-48 hours before the lesions appear, although lesions may be present on the head but covered by hair and not seen during this period.

The incubation period is 14 to 16 days, but it may range from 10 to 21 days or even more in immunocompromised patients or those who have been treated with varicella immunoglobulins.

When the virus reaches a subject, initially it will affect superficial cells of the respiratory and conjunctival mucosae, it will reach regional ganglia, where its first replication will take place two to four days after exposition. It can also reach regional neurons and cranial ganglia, most frequently trigeminous ganglia.

Four to six days after the infection, a primary viremia disseminates the virus, transported by mononuclear cells to other organs, including sensory ganglia, where it will remain latent and may be reactivated years after.

The virus gains access to the neuron by hematogenous spread or by retrograde transaxonal transport from skin vesicles to ganglia, where it will remain latent. During my stay at Columbia University, I had the opportunity to observe a trial with guinea pigs, where it is being proved whether the spread is due to a viremia; occasionally they are vaccinated in one side and the lesions appear on the other side of the animal (data not published).

The virus continues its replication in the infected viscera, and finally a secondary viremia takes place and produces a viral infection of the skin, affecting the skin 14-16 days after the infection, corresponding with the incubation period (10).

In children, the rash is often the first sign of the disease, but in adults there might be a prodrome of 1 or 2 days of fever and malaise preceding the rash. The rash is generalized and progresses from macules to papules, vesicles, pustules and finally crusts. It is characteristic of the disease to present lesions in several stages of development. The rash first appears on the head and goes downwards, affecting afterwards the trunk and finally limbs. The trunk is usually the most affected part of the body, in total they usually have 200 to 500 lesions which are very pruritic. Lesions are 1 to 4 mm in diameter and they can also appear on mucous membranes of the oropharynx, respiratory tract, conjunctiva, vagina or cornea.

Clinically, it is generally a mild disease in children. They have fever up to 39ºC (102ºF) for 2 or 3 days, malaise, pruritus and the typical skin lesions. Children with immunodeficiency, such as HIV, lymphoma or leukemia may develop a severe progressive form of varicella. In adults, the disease may be more severe and with a higher incidence of complications.

Long-term immunity is usually acquired after recovery from primary varicella (11), but a second chickenpox may happen, especially in immunocompromised patients.

2.2.1. Complications.

Complications of varicella infection include secondary bacterial skin infections with Staphylococcus or Streptococcus, which is the most common cause of hospitalization and medical visits (12). This may cause an invasive infection, which is much more severe.

Pneumonia is the most frequent severe complication and it occurs one to six days after the appearance of skin lesions, it is rare in healthy children but causes severe morbidity in healthy adults (13). Meningitis, encephalitis, cerebellar ataxia, diffuse cerebral

involvement and Reye syndrome if aspirin is administered during varicella are other possible complications.

There are other rare complications, more frequent in immunocompromised patients, such as aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, thrombocytopaenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and hepatitis (12, 13).

The risk of complications varies with age, they are infrequent among healthy children, and much more frequent in persons older than 15 years or younger than 1 year of age (10).

In Immunocompromised patients, such as HIV, cancer, bone marrow transplantation, etc., the risk of complications and of disseminated disease is higher than in immunocompetent individuals. They are more likely to be hospitalized for pneumonia than for bacterial skin infection. There may be multiple organ involvement, and the disease may be fulminant (13, 14).

The most frequent complication in adults is pneumonia, which accounts for hospitalization of one in every 400 adults with varicella, and the risk increases with age. Also the mortality is increased with age and varicella can be deadly severe in adults (15).

Several studies have been carried out to analyze the complications and their rates, and are summarized in table 1. Guess et al. in the US, used data from the Commission on Professional and Hospital Activities to determine the most common complication among patients in each age group hospitalized for varicella (15).

Table 1. Most common serious complications among hospitalized patients with varicella (15).

Age (years)	Complications	Estimated number of annual US hospitalizations	Number of hospitalizations/10,000 varicella cases
<5	Bacterial skin infection	320	2.6
	Pneumonia	160	1.3
5-9	Varicella encephalitis	124	0.9
	Reye syndrome	92	0.6
10-14	Reye syndrome	47	1.5
	Varicella encephalitis	28	0.9
15-19	Varicella encephalitis	17	2.9
	Varicella pneumonia	14	2.4
20+	Varicella pneumonia	139	26.7
	Varicella encephalitis	17	3.3

Evidence suggests varicella may be more severe in pregnant woman, especially in the last trimester, than in other adults (16).

During the first trimester of pregnancy, the disease may cause severe embriopathy or fetopathy, but the virus hardly crosses the placenta. An example of this is that only 20-30% of the cases of uncontrolled HIV infected woman transmit the disease to the fetus, and most of the infections are perinatal. On the third trimester, even though the disease is less severe for the baby because the organs are just growing, not developing, the virus crosses more frequently the placenta.

A congenital varicella syndrome is a clinical diagnose of infants whose mothers had varicella during pregnancy. This infection in a pregnant woman may cause damage to the fetal tissues, including the central nervous system, which may result in low birth weight, permanent scarring of the skin, aplasia of the extremities, chorioretinitis,

microphthalmia, optic nerve atrophy, ophthalmic cataracts, Horner's syndrome, blindness, mental retardation, miscarriage and a high incidence of zoster and death in infancy (2). There are also case reports of fetal abnormalities following a maternal herpes zoster (HZ), but congenital syndrome acquired when a pregnant woman has HZ is rare (16).

Infection at any time during fetal life may result in latent infection and reactivate as HZ in early life, but maternal varicella that develops 5 days before to 2 days after delivery is the most serious for the newborn infant, with high fatality rates (16). If the mother develops the disease weeks before delivery, the virus is transmitted but also the antibodies, and on the other hand, if the infection is close to the delivery date, the virus is transmitted, but the antibodies aren't. So, in the days after delivery, protective maternal antibodies to VZV have not yet been formed or crossed the placenta. VZV may cross the placenta during maternal viremia and after delivery the baby is at risk for development of the severe varicella (2). The infected infant may develop hemorrhagic skin lesions and primary varicella pneumonia. This can be avoided with administration of acyclovir (16).

2.3. HERPES ZOSTER. RECURRENT DISEASE.

The VZV remains latent in cranial nerve ganglia, spinal dorsal root ganglia or autonomic ganglia along the entire neuraxis, and it may reactivate and cause herpes zoster, also known as shingles.

When the virus affects the nervous system, it can be found in the cytoplasma of the affected cells, in form of episome, a segment of DNA that can exist and replicate either autonomously in the cytoplasm or as part of a chromosome. It is not integrated, and the mechanism why it becomes latent is uncertain. This stage of latency can last years or even a lifetime, if the immunological capacity of the host does not let the virus replicate (10).

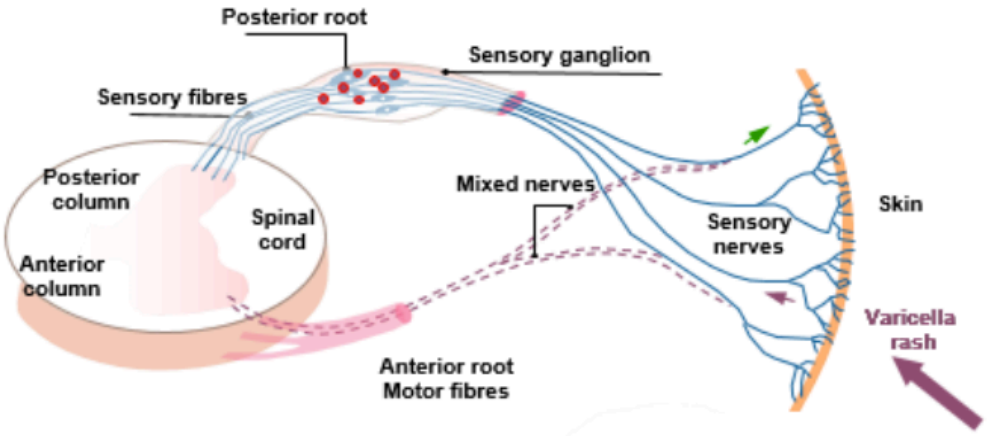

Figure 2. VZV Latency and Reactivation.

The mechanism of reactivation is not well understood. The resurfacing of VZV requires movement of viridions from the neurons, along axons, to the skin, where the virus must evade innate and adaptive host immune responses, spread from cell to cell, and form lesions that eventually penetrate the epidermis. Another theory is that the virus reactivates in the form of a viremia, producing skin lesions not only on a unique dermatome, but also satellite lesions, and can reactivate in other organs (17).

The mechanisms of immune evasion are more successful in the elderly, and other factors may be associated, such as immunosuppression, intrauterine exposure to VZV and having varicella primary infection younger than 18 months (18).

Age decreases the capacity of peripheral-blood T cells. T-cell immunity is started by primary VZV infection and is required for the resolution of varicella. Memory CD4 and CD8 T cells that recognize VZV proteins are present in younger adults, where herpes zoster is rare. An important memory-T-cell immunity may reflect either the extent of the initial expansion during primary infection or periodic boosting on exposure to varicella or on subclinical reactivation. VZV IgG antibodies persist, so people who are at risk for herpes zoster because of declining T-cell responses, continue being protected from varicella. VZV-specific memory T cells probably control the later stages of reactivation, rather than preventing VZV genomes in the ganglia from beginning to replicate (18).

The effectiveness of the Oka vaccine probably results from the restoration of VZV-specific T cells to a level above, enhancing immunity and decreasing the risk of VZV reactivation and HZ lesions (18).

HZ affects the nervous fibers of one spinal root, with a unilateral dermatomal sensory nerve distribution, affecting one to three dermatomes. As we said previously, the most frequent latent state takes place on the trigeminous, but the most frequent reactivation is dorsal. It seems that the virus can be reactivated by a trauma, and traumas in the dorsal zone are more frequent. After radiotheraphy on the head, it can reactivate there, as this treatment is considered a trauma for the skin. It can also affect motor nerves, producing muscular weakness. Rarely, there can also be meningeal affectation. Neurologic damage begins before the characteristic dermatomal rash appears (10).

During reactivation, VZV can be found in saliva of the patients. This was proven in the NASA. They showed the association between VZV reactivation and acute, nonsurgical stress in healthy individuals. This way, we can relate VZV reactivations with facial palsy, zoster sine herpete, and other disorders with unknown cause until today (19).

Clinically, HZ is a vesicular rash on an erythematous base, with a unilateral dermatomal sensory nerve distribution. Pain and paresthesia usually occur prior to the eruption in the area where it will later appear are characteristic. Skin lesions resolve in 1 or two weeks, but pain takes 4 to 6 weeks, and can be followed by chronic pain, known as Post Herpetic Neuralgia (PHN). It is not frequent to develop systemic symptoms (10).

VZV reactivation can also produce chronic radicular pain without rash, also known as zoster sine herpete. All the symptoms may also develop in the absence of rash.

2.3.1. Complications.

Complications of the reactivation can also occur. Chronic pain (PHN), meningitis or meningoencephalitis, cerebellitis, isolated or multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy, mielopahty and inflammatory disorders of the eye (progressive outer retinal necrosis) are some of the most common. The most frequent of them is PHN, which produces pain for months or even years and can affect social and personal life, sleep, or even quality of life (20, 21). More than 50% of zoster patients over 60 years will develop PHN, which may persist for months or even years (22).

2.4. EPIDEMIOLOGY AND INCIDENCE

VZV is worldwide distributed. It is highly contagious and, before vaccination, the lifetime risk of acquiring varicella was over 95%. Over 90% of the cases of varicella were children under 10 years (23). Herpes zoster, on the other hand, primarily affects the elderly population. Reactivation occurs in 15-25% of individuals, of which over 70% are adults.

2.4.1. Varicella.

Before the vaccination program, annual varicella incidence in the United States was 1500-1600 cases per 100,000 persons per year. In Spain, the average number of cases declared was 479.31 per 100,000 persons per year. There were two clear epidemic waves, with higher incidence in 1999 and 2004 (24).

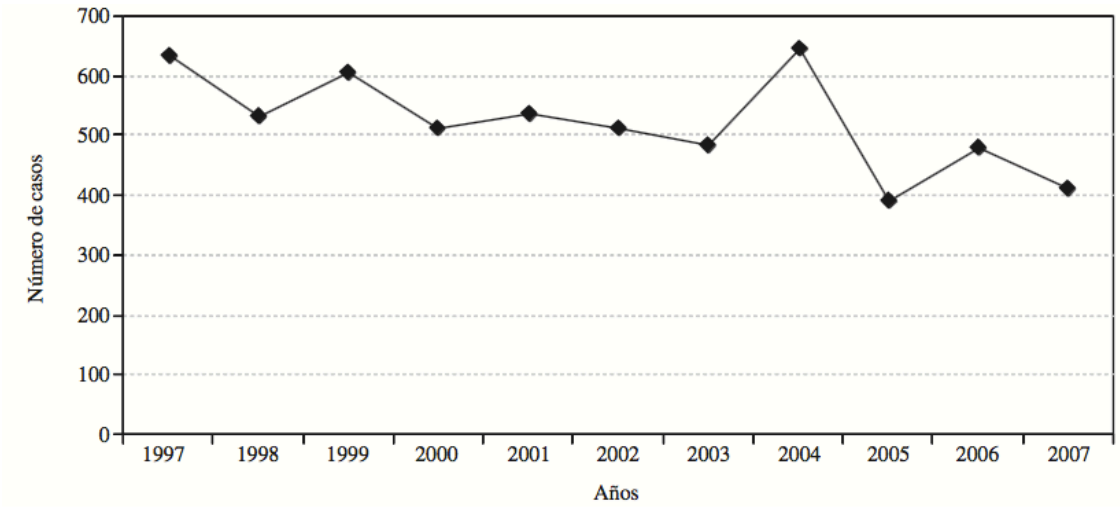

Figure 3. Incidence of varicella per 100,000 persons per year in Spain 1997-2007 (24).

2.4.1.1. Age distribution.

In 2007, Peña-Rey et al reported the varicella epidemiology in Spain. The age distribution of varicella described was (24):

- 88.1% of the cases in children under 15 years, of which:
  - 79.8% in 1 to 9 years

        - 1-4 years 50.6%
        - 4-9 years 29.2%
    - 4.5% under 1 year
- 9.9% in subjects 15 to 44 years of age
- 1.1% in older than 44 years.

There is a clear difference between incidence of varicella in children and adults in industrialized countries, were children have a higher incidence of varicella but less complications. The data shown above can be seen in other studies and CMBD data analysis (24).

Reports from tropical countries indicate a significant incidence of varicella among adults. A study carried out in India and published in 1998, studied adult Bengalee population living in urban and rural area with identical climatic conditions, belonging to the same social level, but urban people were living in clusters. 3.4% of urban adults were seronegative, compared with 31.1% of rural adults. The results suggest that a significant number of subjects living in the rural area do not contract varicella until they are adults due to the low contact, while urban adults are immune as a result of earlier infection (25).

2.4.1.2. Hospitalizations.

2.4.1.2.1. Spain.

A study collecting data from 1995-2000 described the hospitalization rates of varicella for all ages, the mean incidence was 2.7 cases per 100,000 persons per year in Spain, with differences among communities, being highest in Navarra with 3.2 per 100,000 persons per year and lowest in Canary Islands with 1.5 per 100,000 persons per year (26).

The same team, using similar methdoogy and collecting data from 1999-2000, before the vaccine was available and using the national minimum basic data set (CMBD), reported an average hospitalization rate of 3.1 per 100,000 persons per year and 600 per 100,000 cases of varicella. These figures are slightly higher and reflects the annual

variability as shown in Figure 3. From this study we can estimate that about 0.6% of the cases of cases of varicella were hospitalized in Spain. During 2004 the hospitalization rate reached 4.2 per 100,000 persons per year (27).

2.4.1.2.2. Age variation.

Hospitalizations in children are more frequent in infants under 1 year, followed by children 1 - 4 years. In any of the cases, there is no difference between women and men (24).

Guillen et al. published two different studies where the rate of hospitalization during 7 years was evaluated. For children under 14 years, during the 7-year period of 1999-2005, there were 23.06 hospitalizations per 100,000 persons per year (28), while in adults older than 18 years, for the period of 2001-2007, there were 2.2 hospitalizations per 100,000 persons per year (29).

2.4.1.2.3. Complications.

Of the hospitalized patients, an average of 49% had complications, that increased with age (24):

- 38% in children under 14 years
- 56% in 15 years or older
- 65% in adults aged 25 to 34.
- 69% in adults 35 - 44 years

The most frequent complication was pneumonitis, described in 26% of hospitalized patients for varicella, being 43% in adults and 9% in children under 14 years. Encephalitis was present in 4.6% of hospitalized patients and it was more frequent in children (7.1%), than in adults (3.5%). Other complications had a rate of 18.2% of the patients (24).

The average length of hospitalization for varicella was 6.5 days and 90% of the cases were hospitalized less than 11 days. There were 742 cases of nosocomial varicella (15.5 cases per 100,000 total discharges). The hospitalized patients for any other reasons rather than varicella, that developed a nosocomial varicella had a mean length of

hospitalization of 8.5 days, and 90% of the cases stayed less than 17 days at the hospital (24).

2.4.1.3. Risk groups.

Risk groups are groups of people who have a higher probability of developing a severe or complicated varicella. In the Valencian Community the risk groups that are considered for varicella vaccination are susceptible individuals with a primary or secondary immunodeficiency (VIH, acute lymphoblastic leukemia, high dose steroids, radiotherapy, etc.), with a chronic disease (cystic fibrosis or severe disseminated skin disease), or subjects in contact with high risk groups (30).

2.4.1.4. Seasonal fluctuation.

Varicella is considered a childhood disease that varies with climate, but it differs from some countries to others. Different hypothesis may explain this; either there are climatic variations in the transmission effect, or transmission is related to routines (31, 32).

In Spain, the pattern has the highest incidence at the end of spring and beginning of summer, corresponding with the epidemiological pattern of temperate climate areas (33).

Varicella, unlike herpes zoster, has seasonal fluctuations. In the North hemisphere, the highest incidence is between March and May, and lowest between September and November (10).

2.4.1.5. Mortality.

Although varicella is usually considered a mild disease, occasionally can complicate and result in death. In pre-vaccine era, varicella caused 50-100 deaths per year in children less than 15 years of age in the United States, with higher lethality in infants and in adults (34).

In Spain, during the decade of 1997 to 2007, deaths caused by varicella varied from 4 to 14 per year, with an annual rate of 0.02 deaths per 100,000 persons per year and a

lethality of 4.8 deaths per 100,000 varicella cases. 80% of them were in patients older than 25 years, with the highest concentration between 25 and 44 years. The highest mortality incidences were registered in patients in the following age groups: under 4 years, between 25 and 44 years and older than 65 years (24).

Table 2 shows the incidence of disease, hospitalization and lethality in Spain. The highest case-fatality rate was in older than 50 years. This is due to the higher number of complications, the severity of the disease at older ages and immunodeficiency in these patients.

Table 2. Age-specific average annual number of hospitalizations, deaths, incidence and case-fatality for primary varicella in Spain (27).

Age group (years)	Average number of hospitalizations	Incidence (100,000 persons)	Average number of deaths	Case-fatality rate
<1	225	60.3	0	0
1-2	149	20.3	0	0
3-5	359	32.8	1	0.3
6-10	171	9.2	0.5	0.3
11-20	76	1.7	2	2.6
21-30	159	2.6	1	0.6
31-50	316	2.9	4.5	1.4
>50	89	0.7	6.5	7.3
Total	1542	4.1	15.5	1.0

2.4.2. Herpes zoster.

A recent systematic review, including 130 different studies from 16 countries, concluded that the incidence rate of HZ ranges from 3 to 5 per 1000 person/year in North America, Europe and Asia-Pacific (35).

2.4.2.1. Spain.

In total, 30% of the population will suffer HZ during their life (35). Two thirds of the cases occur in subjects over 50 years of age, and is more frequent in women. In Spain, in 2007, 87% of the cases were older than 25 years and 3.7% under 9 years (24).

In Valencia with a population of around 5 million inhabitants, a study during 2007-2010 concluded there was a total of 85,586 cases, with an average rate of 4.60 per 1000 person/year. It was more frequent in women and with a peak incidence at 70-79 years. 7.16 per 1000 cases of HZ required hospitalization (36, 37).

2.4.2.2. Complications.

HZ Complications increase with age, but they occur in up to 50% of the cases, including PHN, which occurs in 10-15% of the patients, and in 28% of the older than 70 years (24).

A study in Spain (1998-2004), showed an incidence of hospitalizations of HZ of 13.4 cases per 100,000 persons per year (38). Another study, by the same group, from 1999-2000, showed an incidence of hospitalizations of 8.4 cases per 100,000 persons per year of HZ and its complications, depicted in Table 3 (27).

Table 3 Age-specific average annual number of hospitalizations, deaths, incidence and case-fatality for HZ.

Age group (years)	Average number of hospitalizations	Incidence HZ (100,000 persons)	Average number of deaths	Case-fatality rate
0-14	98	1.7	0	0
15-20	32	1.1	0.5	1.6
21-30	94	1.5	0.5	0.5
31-50	465	4.3	11	2.4
>50	2474	20.8	103	4.16
Total	3162	8.4	115	3.6

The hospitalization rate for HZ in 1997 to 2007 in Spain was 2.5 per 100,000 persons per year with important variations among regions (24, 38), and by age: 2.7 per 100,000 persons per year in older than 14 years and 1.03 per 100,000 persons per year in under 15 years. The average annual rate of HZ in patients hospitalized by other causes with a nosocomial HZ was 44.03 per 100,000 hospitalized patients, 87% older than 45 years (24).

There is a difference in the incidence of HZ in these studies (13.4 vs 8.4 vs 2.5 cases per 100,000 persons per year), even though they are based on the information from the same databases. This might be explained because the period of time they studied is variable, but only considers several Regions, but most importantly, it is probably explained because they used different methodologic strategies.

In Spain, the length of hospitalization due to HZ was 9 days, while patients who were admitted at the hospital for other reasons and during their stay developed HZ, was 14.5 days.

2.4.2.3. Mortality.

In Spain, during the years 1997 and 2007, there were a total of 145 deaths associated to the diagnostic code of HZ. Per year there were between 12 and 23 deaths with an average rate of 0.29 deaths per 100,000 persons per year. 95% of them were older than 70 years and 80% older than 80 years. Under 45 years of age there was only 1 death due to herpes zoster (24).

2.5. VARICELLA VACCINE.

There are three VZV-containing vaccines licensed: varicella vaccine, combination measles-mumps-rubella-varicella (MMRV) vaccine, and herpes zoster vaccine.

2.5.1. Live viral vaccines.

Live viral vaccines contain attenuated virus, so this vaccine strain replicates and infects the organisms but do not cause disease, therefore they act as a natural infection and stimulate strong cellular and antibody responses and often confer lifelong immunity without posing the threat of the wild type virus.

Attenuation was achieved in a lab by incapacitating the epitopes which allow a virus to cause damage in the human host. There are several ways of attenuation. The strains can be altered by passage in vitro in human cells or by growing in chick or duck embryo cells. The virus can also be adapted to grow in unnatural conditions such as cold temperature to reduce its ability to grow and replicate in the normal conditions of the human host. As they evolve to adapt to the new environment, they become weaker with respect to their natural host, human beings (2).

Attenuation is considered successful if the manipulated virus retains its infectivity at the site of inoculation and provokes an effective immune response, but lacks its ability to replicate further and present a threat to the health of the recipient.

The goal of vaccination against viral pathogens is to elicit protective immunity and immunologic memory in the host so that an immune response will occur upon future exposure to the wild type virus.

2.5.2. Varicella vaccine.

Varicella vaccine is an attenuated viral vaccine, and is the first one to be used for the prevention of a virus capable of establishing latency in the human host.

2.5.3. History.

As vaccine technology improved, interest in preventing varicella by immunization grew. The first reason was that varicella often causes severe disease in adults, infants, and immunocompromised patients, resulting in extended hospital stays, deaths, and other problems. Second, control of varicella using antiviral drugs was not feasible as these medications were still in the primary phases of development. Finally, the great volume of cases of varicella guaranteed significant morbidity and mortality despite the usually benign nature of the disease.

Initially, a candidate vaccine strain called KMcC was developed in human diploid cells and underwent a few clinical trials (39). However, it was not possible to obtain a vaccine with this strain with low reactogenicity and high efficacy. This means that the virus could not be attenuated to stimulate enough immune response to provide protective immunity against varicella. This strain is no longer being studied or used.

Michiaki Takahashi, for the Biken Institute of Japan, developed the first successful varicella vaccine in 1974 (40). Takahashi was the only researcher to add an extra step to the process of attenuation that achieved the desired balance of safety and immunogenicity using the Oka strain.

Originally, the interest in varicella vaccine was related to prevent the disease in leukemic children, as they were starting to survive beyond diagnosis due to chemotherapy advances. Many of these children, were exposed to varicella, and developed a severe varicella that sometimes even lead to death. Therefore, the original goal of the varicella vaccine was to reduce morbidity and mortality in leukemic children.

Takahashi first tested his vaccine in healthy children during a varicella epidemic at a hospital in Japan (41). It seemed to stop the outbreak and to have very few side effects.

He continued to test this vaccine during the next four years (42) and finally he moved on and began clinical trials in immunocompromised children. Even in this group, the vaccine was found to be safe and effective except in children with lymphomas (43, 44).

After the success of the vaccine, the interest in varicella vaccine grew in the United States. They were prepared to conduct clinical trials similar or even more extensive than those completed in Japan (45, 46). The efficacy and safety of the vaccine could be evaluated with PCR that could determine if a varicella disease was caused by a wild type or by a vaccine strain virus.

Initially a request to do clinical trials of the varicella vaccine was submitted to the National Institute of Health (NIH) and in 1979, Dr. Anne Gershon and colleagues received a grant from the National Institute of Allergy and Infectious Diseases (NIAID) to conduct multi-centered clinical trials at New York University Bellevue Hospital Medical Center. They started with healthy adults, and soon they vaccinated leukemic children who could complete chemotherapy treatment (47). Their last step was vaccinating leukemic children still receiving maintenance chemotherapy. Some of them developed breakthrough varicella, and they used antiviral medication to minimize the rashes.

The NIAID Varicella Vaccine Study Group (in collaboration with Columbia University and over 20 medical centers in the United States and Canada) immunized 575 children with leukemia and 372 healthy adults with no prior history of varicella over the next 11 years, and evaluated the safety, immunogenicity, and protective efficacy. Follow-up of vaccines continued for years (48).

The vaccine was safe and highly immunogenic in all groups tested. They found out that two doses of the vaccine in adults and leukemic children, had superior immunogenicity. The study group also found that a mild vaccine-associated rash in the first six weeks after vaccination occurred in 5% of healthy vaccinees and in 10-40% of leukemic vaccinees. In the leukemic vaccinees the risk of rash is 40% after the first dose and 10% after the second dose. Although most of the rashes in the leukemia vaccinees were mild, some were treated with antivirals (47).

As the results of the vaccine were so encouraging, the main goal of the program began to shift from vaccinating high risk individuals to eradicating and preventing the disease in the entire population. Furthermore, the best way to protect high risk individuals was to decrease the chance of exposure by immunizing the healthy population.

In 1995 the FDA licensed the varicella vaccine for use in healthy children in the United States. Since then, varicella vaccine has been recommended in many countries and very successful decreasing varicella cases and reducing severe disease in high risk patients.

2.5.4. Current vaccine.

The currently used varicella vaccine is prepared with the Oka strain of live, attenuated varicella virus.

The Oka strain varicella vaccine was developed following a number of steps.

1. Fluid was taken from the vesicles of an otherwise healthy 3-year old boy with chickenpox, whose family name was Oka, and this is the reason for its name. The strain from the wild-type VZV was called Oka-P. Initially it was prepared according to the classical method of vaccine attenuation.
2. The virus was isolated in primary Human Embryo Lung Fibroblasts (HELF) cell cultures with 11 serial cultivations.
3. Then, they were attenuated by 12 passages in guinea pig fibroblast cells (GPFC).
4. Finally, propagation took place in human diploid cell cultures, yielding Oka-V (41). The strain is marketed by Merck under the name of VarivaxTM or Oka/Merck, by GSK as VarilrixTM, and also by BCHT Biotechnology.

2.5.4.1. Oka vs wild strain.

In USA and Europe, only the Oka strain is used for vaccine manufacturing. There are ample differences between the Oka strain and wild-type VZV. Sequence differences are particularly in ORF 62, which is responsible for viral growth and movement from infected to uninfected cells, but it is not known if any of these mutations are responsible for

attenuation (49). Clinically, PCR and restriction endonuclease digestion of the resulting DNA fragments can distinguish between both VZV types.

It is important to distinguish vaccine or wild strains of VZV in recently vaccinated patients with rash or neurologic events and in zoster in vaccinated patients to determine if they are related to the Oka strain or to a wild virus.

2.5.4.2. Attenuation.

The evidence of attenuation of the varicella vaccine is clinical. The incidence of rash following vaccination is lower than the incidence of rash following natural infections (50). The rash that may occur following vaccination is milder than a wild virus varicella, usually having few lesions.

The vaccine virus may be transmitted to a healthy susceptible person, and the disease then is mild or subclinical (51). Besides, the rate of transmissibility of Oka in leukemic vaccinees was lower than that of wild-type (52). There is no evidence of clinical reversion of the Oka strain to virulence.

2.5.4.3. Constituents.

In order to prepare a vaccine, infected cells are harvested, suspended in the vaccine medium and exposed to a high-speed jam stream that breaks the cells to obtain cell-free virus.

The vaccine medium usually contains sucrose and buffering salts. It is sold in a lyophilized form to improve stability. It must be reconstructed with sterile distilled water, which is provided with the vaccine (53).

2.5.5. Vaccine Efficacy and Effectiveness.

2.5.5.1. Pre-licensure efficacy.

The first published study of varicella vaccine efficacy, immunization was used to terminate a potential outbreak of nosocomial chickenpox (41). Healthy children were immunized: no further cases of varicella occurred and they were protected after four subsequent hospital exposures to varicella. These data suggested that the live, attenuated varicella vaccine would be effective in preventing the disease.

There were two double-blind, placebo-controlled efficacy studies carried out in Europe and in the United States in healthy subjects. Other studies took place in Japan and elsewhere.

The first one took place in Philadelphia in the early 1980s, with Merck's Oka vaccine. In this study, the vaccine efficacy to prevent varicella was 100%. After vaccination, none of the vaccine recipients who were exposed to varicella developed the disease, so it was 100% efficacious. After a 7-year follow-up, 95% of the participants remained free of varicella (45).

The second study took place in Finland with the GSK vaccine. The efficacy calculated was 88% in the high-dose group (10^4.0 (10,000) and 10^4.2 (15,850) pfu/dose) and 55% in the low-dose group (10^3.1 (1260) and 10^2.8 (630) pfu/dose). The varicella in vaccinees was milder than those on placebo group, and is called breakthrough varicella (46).

2.5.5.2. Postlicensure effectiveness.

Vaccine effectiveness has been studied by many methods, in different settings, and with different case definitions. Most of the studies analyzed the Merck varicella vaccine in the US vaccination program.

The first published post-licensure study was conducted during an outbreak in a day care setting. By the end of the outbreak, 88% of unvaccinated children had varicella,

compared with 14% of vaccinated children, which makes an effectiveness against the disease of 86% and of 100% on preventing moderate and severe varicella (54).

The estimated effectiveness in the different studies ranges between 80 and 85%. A 2008 review of 17 different studies in the USA demonstrated that one dose of varicella was 84.5% effective in preventing all varicella and 100% effective in preventing severe varicella (55).

In 1995 the vaccine was licensed for individuals older than 12 months of age. Although there was a decrease in varicella in US and Canada after the introduction of routine 1-dose varicella vaccination, there were still some concerns. Varicella outbreaks continued occurring in highly vaccinated populations, and the one dose vaccine was observed to be 80-85% effective with time.

A study measured the efficacy of 2 doses of varicella vaccine comparing it to 1-dose for a 10-year period (56). The efficacy for 2 doses was significantly higher (98% vs 94%), so the US Advisory Committee on Immunization Practices (ACIP) adopted a recommendation in June 2006 that children between 4 and 6 years of age should receive a second dose of varicella vaccine (57, 58).

In Navarra, Spain, in children aged one to eight years, the incidence of varicella after universal vaccination decreased by 98.5%. In cohorts vaccinated at age 10 to 21 years, the incidence decreased by 93.8% until 16 years of age and 90.1% in patients aged 17 to 21 years. In total, effectiveness of at least one dose of varicella was 96.8% (59). In unvaccinated age groups, there was also a reduction of 90.5% in infants under one year of age and 89.4% in nine-year olds due to herd immunity. In people over 21 years, the reduction was 92.4% (59).

In this study, 10.6% of varicella cases were in vaccinated children. 0.9% were considered vaccine cases and 9.7% vaccine failures or breakthrough cases, considering it to be a case of varicella that appears in a person who was vaccinated more than 42 days before the onset of symptoms. Therefore, a total of 0.56% of the varicella cases were

breakthrough varicella cases, and of the vaccine failures 1.38% of one dose vaccinated failed, and 0.13% of those with a second dose had a varicella outbreak (59).

Similar results were described in the USA, where breakthrough varicella cases were only occurred after the first dose. No case was reported after dose 2. The total number of breakthrough cases during the 14 years of follow-up was 15.9 per 1000 persons per year, but only 0.3 per 1000 persons per year for more than 300 lesions. This study in Northern California compared incidence of varicella and HZ post vaccine and pre-vaccine era. The incidence of varicella was 9 to 10 times lower than historical rates prevaccine era. The global effectiveness of varicella vaccine was 89 to 90% (60).

It is also important to know which program is most effective, a one or a two dose vaccine program. A mathematical model estimated that, assuming 90% coverage, 1-dose vaccination will reduce varicella and zoster cases by 64% and 5% respectively. A second dose would add a 22% and a 6% reduction. In total, the reduction estimated is of 90% and 10% in over 80 year old people (57). Thus, they concluded that a 2-dose regimen of varicella vaccination should be recommended for healthy infants and children. This would prevent from becoming susceptible patients who had a primary vaccine failure or weak response (61).

2.5.5.3. Breakthrough varicella.

Breakthrough varicella is varicella developing more than 42 days after immunization.

About 10-15% of vaccinees do not acquire complete protection and can develop a breakthrough varicella (62). The reporting rate was 1 case per 10,000 doses of vaccine, with only 11% having more than 300 lesions (51). A PCR in these cases can differentiate between wild type varicella virus or Oka varicella.

There have been several severe complications due to varicella vaccine, including hospitalizations, cellulitis, ataxia, meningitis, fever, and extensive case in a patient on chemotherapy for neuroblastoma. Two deaths due to breakthrough varicella have been described so far: one in a 9-year-old girl with asthma while on treatment with steroids

and a 7-year-old girl with malignant ependymoma on treatment with dexamethasone (51).

Vaccinated individuals with breakthrough, may transmit the wild-type virus to varicella-susceptible individuals. It is rare that the Oka strain is transmitted from person to person. The transmission rate from breakthrough vaccinated individuals to unvaccinated individuals was 37.1%, which is half the transmission from unvaccinated varicella to unvaccinated, which is 71.5% (63).

2.5.5.4. Herpes zoster after vaccination.

In 1965, Hope-Simpson published a hypothesis about the pathogenesis of herpes zoster (1). He suggested that some factors could interfere in the decline of immunity and prolong the latent interval. He hypothesized that each reactivation of the virus in the ganglia is likely to stimulate antibody production. Antibody values are high after varicella, but they decrease with time, and it is possible that a secondary stimulation may cause an elevation of antibody content. He linked viral replication and clinical disease to an increase of immunity, which controls replication and reactivation of the virus, maintaining it subclinical and asymptomatic by contained reversions. He described the possibility that the boosts are due to extraneous stimulation: each time a person who has had varicella encounters an infectious case of varicella or zoster, he may get in contact with the virus and this might boost his immunity.

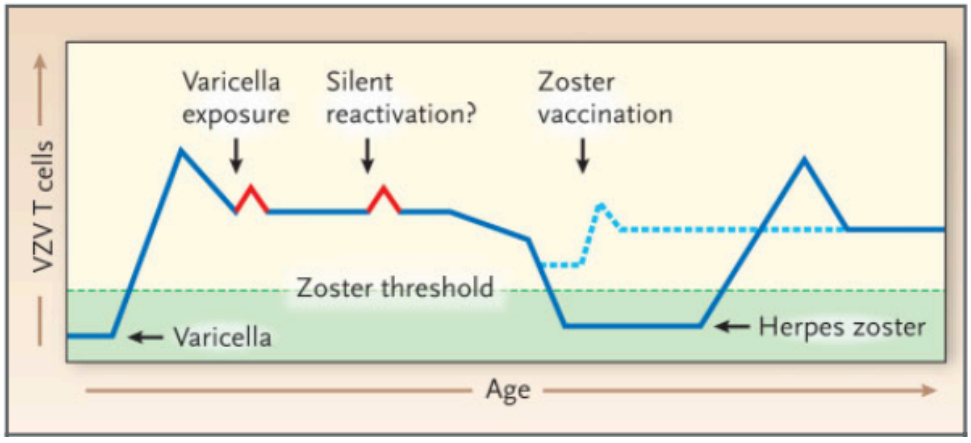

Figure 4. Pathogenesis of zoster. Modified from (1).

Based on Hope-Simpson's hypothesis, Brisson et al. created a model to simulate varicella dynamics and HZ after universal childhood vaccination. They predicted an increase in zoster cases following the near elimination of varicella cases due to vaccination occurring in young adults several years following the varicella program. They concluded that very effective programs in terms of varicella reduction could be harmful to public health in terms of zoster morbidity (64).

There is an open debate about how varicella vaccination may modify the incidence of herpes zoster. There are studies that demonstrate an increase of HZ after the varicella vaccine was recommended (65). Other studies cannot find these results and CDC authorities claimed there was no increase on the incidence of HZ in any US surveillance site; Goldman wrote there was an increase in the HZ incidence rate among children and adults with prior history of natural varicella by the year 2002 (65).

There are examples against this hypothesis, for instance a study developed in France and observing incidence of zoster in cloistered nuns and monks without contact with children and general population demonstrated there has not been a change in the slope of the increase of zoster. It seems that the incidence of zoster is rising because immunosuppression is increasing and population is ageing, as both populations had the same incidence (66), this study has been criticized among others by its low sample size.

A systematic review published in 2013 analyzed 40 different studies and concluded that exogenous boosting exists, although not for all persons, nor in all situations. Its magnitude is yet to be determined adequately (67).

It seems that initially in the United States there was an increase on the global incidence of shingles, although there seems to be a decrease of HZ in vaccinated children under 10 years of age (68). Healthy immunized children have a decrease in HZ incidence compared to unimmunized children (68-70). The incidence of HZ in vaccinated children in Northern California suggested a decrease of approximately 40% compared to pre-vaccine rates of HZ. The incidence did not increase in any age category (60). Another significant advantage of vaccination is that in leukemic children it leads to a lower incidence of zoster than after natural chickenpox (48).

Globally, in children under 10 years and adolescents, HZ incidence from 2000 to 2006 in California declined by 55%, and children with a history of varicella vaccination had 4 to 12 times lower risk of developing herpes zoster compared with children with history of varicella disease (70).

There is also a global concern that the vaccine strain can establish latency the same way the wild virus does and that it can reactivate and cause HZ in vaccinees. However, very few cases of this type of HZ have been documented.

To summarize, different observational studies show no consistent trends in HZ incidence in the United States since the varicella vaccine program started.

2.5.6. Adverse events.

The most common adverse events reported in pre-licensure studies were mild and self limited. The most common were tenderness and redness at the injection site (15-20% of vaccinees), fever (about 14%), and mild rash (4%). The only difference with placebo recipients was pain and redness at the injection site (45).

After vaccination, healthy children may develop lesions similar to varicella. It is considered that if they develop less than 10 lesions, it could be a varicella-like reaction due to the vaccine. If there are more than 30 lesions within the first 2 weeks after the injection, we could suspect wild-type strain intercurrent infection.

There have been several post-licensure studies that have proven the safety of the varicella vaccine after more than 10 years of use in the United States:

The Vaccine Adverse Event Reporting System (VAERS), after 16 million doses published that the rate of adverse events was 67.5 per 100,000 doses and 2.9 severe adverse events per 100,000 doses (71).

Recent studies demonstrate that serious adverse events are rare, and events that have been reported include encephalitis, ataxia, erythema multiforme, thrombocytopenia,

recurrent popular urticarial, anaphylaxis, stroke and transverse myelitis. None of these events were proven to be caused by the vaccine virus (51).

There are very rare complications caused by the varicella vaccine Oka strain, like pneumonia, hepatitis, herpes zoster, meningitis, severe rash and secondary transmission (51).

2.5.7. Present situation.

In the United States, the vaccine is in the National Immunization Program since 1996. Several studies calculate an efficacy of about 75% for the disease and 99% for moderate and severe varicella (55). Globally in the US, the incidence, complications, hospitalizations and death rate due to varicella have decreased.

2.5.7.1. Vaccination in Europe.

But even though in the USA the results of universal vaccination have been impressive, in most of the European countries the vaccine is not recommended. There are several reasons for this (72):

- Lack of recognition of the severity of the disease: in some countries it is still not a notifiable disease, and therefore there is a lack of consciousness about potential complications and patients and doctors still see the disease as benign.
- Perception that the disease will shift to older age patients: It has been said that universal vaccination may produce an increase of varicella cases in patients of older age, where the disease is more severe. In the USA, after the introduction of vaccination, there has been an increase in the percentage of older children that have the disease (as it is decreasing in younger children), but there has not been an increase in hospitalizations or global incidence of varicella for any age group (including non-vaccinated children and adults).
- Potential increase of herpes zoster perception in unvaccinated adults.

2.5.7.2. Vaccination in Spain.

In 2004 varicella vaccine was licensed in Spain. In two of the autonomous communities, Madrid and Navarra, a universal vaccination of infants aged 1 year and 1 and 3 years respectively, was started, with reported benefits. In Madrid, in spite of the clear benefits, the vaccine was withdrawn for political reasons in 2013, and resumed in 2016.

In the rest of the Communities, the program included vaccinating 11 to 12-year-old subjects with no history of varicella or varicella vaccination, with the objective of decreasing varicella cases in adults. Apart from this program, pediatricians recommended the vaccine (Spanish Pediatric Association recommendation), and parents could vaccinate the children outside of the national vaccination program, by paying for a two-dose schedule at 12 months and 3 years of age.

Vaccination coverage in the young ages reached 50-60%, depending on the Communities. (73)

In 2013, the Spanish Agency of Medicines blocked the vaccine distribution based on a partial coverage of the vaccine that hypothetically could induce an increase of cases in adults, as unvaccinated children may reach adulthood without having had contact with the virus (in case the herd immunity stopped the virus circulation), or a hypothetical loss of vaccine protection in the long run. Also, this measure wanted to avoid increasing the number of cases of herpes zoster in adults.

In 2015, varicella vaccine was commercialized again, and then included in the Immunization Schedules of Spain.

2.6. ECONOMIC ANALYSIS

Vaccination is an effective and safe intervention for prevention of infectious diseases. It brings benefits to the vaccinated subjects and indirectly to the whole community by inducing protection to non-vaccinated: herd immunity.

The WHO recommends that routine childhood immunization should be considered in countries where the disease is a relatively important public health and socioeconomic problem, the vaccine is affordable and high and sustained coverage can be achieved (62).

In developing countries, or with limited resources, their concern is preventing diseases with higher morbidity and mortality.

In developed countries, the cost-effectiveness of vaccination must be evaluated as further data are required for implementation of a universal vaccination program.

Many studies have shown that varicella vaccination would be cost-effective from societal perspective. Not all, but many have demonstrated it would also be cost effective from the health payer's perspective. There have been several reviews that evaluate these different studies (62, 74, 75).

In some countries, varicella disease means a large economic burden on society with high direct costs but also indirect costs. But there are different situations depending on the country, for example, in Germany, work loss cost of the parents of infected children are paid by the government. In this case, varicella vaccination would be beneficial to the society and health care payers (76).

In the next table we can find a review of different studies in different developed countries around the world.

Table 4. Worldwide Cost-effective studies of Varicella Vaccine.

Authors	Year	Country	Main results
Scuffham et al. (77)	1999	New Zealand	Average saving to society of childhood vaccination is high, but it does not confer savings in terms of health care costs alone.
Diez-Domingo et al. (78)	1999	Spain	Universal immunization of infants is cost beneficial if indirect costs are taken into consideration.
Coudeville et al. (79)	1999	France	Co-administration of varicella and MMR vaccines to healthy children produces a net benefit from a societal perspective.
Scuffham et al. (80)	2000	Australia	Infant immunization is the most cost-effective strategy analyzed.
Brisson et al. (81)	2002	Canada	From a societal perspective, mass infant vaccination is highly cost-saving. From a health payers perspective, routine vaccination at 12 years is cost-effective.
Wutzler et al. (82)	2002	Germany	The most favorable: children and combined MMRV vaccination.
Getsios et al. (83)	2002	Canada	Children 1 year with or without catch up, overall cost will reduce but to the health care system will increase.
Hai-chun Hsu et al. (2)	2003	Taiwan	Benefit-cost ratio positive, specially from the societal viewpoint. Net savings with indirect costs.
Brisson et al. (84)	2003	England and Wales	Adolescent strategy is cost saving. Infant and catch up strategy no.

Banz et al. (76)	2003	Germany	Routine children vaccination would be cost saving for the society and for the payer's perspective. Adolescent vaccination is also cost saving from societal perspective.
Hanslik et al. (85)	2003	France	With serotesting and vaccine in young adults, compared with no intervention, it is not cost beneficial. Without serotesting, costs increase even more. From societal perspective it might save costs.
Thiry et al. (86)	2004	Italy	Compulsory vaccination of 11 year olds saves costs.
Ginsberg et al. (87)	2004	Israel	Vaccine susceptible 1 year old reduces direct costs and benefits the health services.
Jean-Jasmin et al. (88)	2004	Singapore	Universal vaccination was cost beneficial, mainly from societal perspective.
Coudeville et al. (89)	2004	Italy	Routine vaccination could induce savings and be cost effective from societal and health-system perspective. If combined with catch-up programs, there would be further cost reductions.
Coudeville et al. (90)	2005	France and Germany	For high coverage rates, routine vaccination induces savings in both countries from societal and third-party payer perspectives. For low coverage rates, not from third-party payer in France.

Lenne et al. (91)	2006	Spain	Routine varicella vaccination is cost-saving from societal perspective and highly cost-effective for Health Care System.
Hammerschmidt et al. (92)	2007	Germany	Universal vaccination and catch –up vaccination reduces cases, complications and hospitalizations.
Valentim et al. (93)	2008	Brazil	Cost-effective per life-year saved under societal and healthcare system's perspective.
Bonanni et al. (94)	2008	Italy	Vaccine toddlers and adolescents resulted in the highest annual net savings. Not from national health system.
Zhou et al. (95)	2008	USA	1-dose and 2-dose program were cost saving from societal perspective. The second dose was not cost saving from payers view.
Banz et al. (96)	2009	Switzerland	Universal childhood vaccination with or without catch up results in net savings from societal perspective, not from payer's perspective.
Van Hoek et al. (97)	2012	United Kingdom	Cost-effective with a combined policy influenced by benefits that accrue decades after start of vaccination. In a short time frame, not so cost-effective.
Bilcke et al. (98)	2013	Belgium	In a long time period, different options for universal vaccination would be cost-effective.

In Spain, one study in 1999 analyzed the economic impact of varicella vaccination in children, where a static model was used to estimate the costs and effects of vaccination without considering herd immunity effects (78). Another study in 2006, evaluated the epidemiological and socio-economic consequences of a routine childhood vaccination program in Spain with the Oka/Merck varicella vaccine by using a dynamic model, which considers herd immunity effects (91).

The results of this last study were that from the societal perspective, the routine vaccination was cost-saving whether or not indirect costs are considered. From the Health Care System, the strategy was also cost-effective, although it leads to a small increase in costs (91).

2.7. PREVIOUS MODELS.

Several models have been created previously, and they have been the base for many other studies in different countries around the world.

There are several main mathematical models that have been used, such as the model developed by Halloran published in 1994 (99) and Brisson's model published in 2000 (64). Garnett developed the first model that explored the relationship between varicella and zoster (100, 101). Other models, such as Karhunen from 2010 (102) have also been used.

Garnett and Grenfeld examined the impact of vaccination on the long-term equilibrium incidence of these diseases, but ignored the possible short to medium term (64). They reviewed and discussed the different hypotheses of virus reactivation. They developed a mathematical model of primary disease and reactivated disease in developed countries. The steady state age distributions of zoster cases predicted by the model were compared with observed distribution of published epidemiological data. The model allowed differentiation between published hypotheses in which age of host may or may not influence the probability of viral reactivation. The results indicated probability would increase with age, and this is the cause of the observed pattern of zoster cases (100). They used the model and data analysis to examine the epidemiological implications of varicella immunization and herpes zoster. The analysis of data provided indirect evidence for the hypothesis that a high intensity of varicella transmission suppressed viral reactivation. The mathematical model took into consideration the influence of the prevalence of varicella on viral reactivation and the impact of vaccination with attenuated virus. Under some conditions, mass vaccination may have impact of increasing zoster incidence (101).

Halloran's model was published in 1994. This model was a transmission non-linear, age-structured, deterministic model. The values for vaccine efficacy were based on a review of the literature by an expert panel. Their results were that although implementation of a vaccination program resulted in a shift in the age distribution of remaining varicella cases toward older ages with higher complication rates, the overall reduction in cases

resulted in decreased morbidity measured by number of hospitalizations and primary cases. Routine immunization would result in reduction of uncomplicated and complicated chickenpox cases (99). Table 5 shows different studies based on Halloran's model.

Table 5. Models and studies based on Halloran's model.

Author	Year	Countries	Model	Results
Lieu et al. (103)	1994	US	Used Halloran's mathematical model of vaccine efficacy for clinical outcomes.	A routine varicella vaccination would prevent 94% cases of chickenpox, from societal perspective it would save money, but not from health care payer's perspective.
Banz et al. (76)	2003	Germany	Age-structured, decision analytic model to compare potential clinical and economic effects of varicella vaccination strategies compared to no vaccination. Transmission model based on Hallorans.	Routine childhood varicella vaccination appears to be highly efficient strategy to reduce the burden of varicella and results in significant savings for both the society and the payers.
Coudeville et al. (89)	2004	Italy	Epidemiological model of VZV dynamics adapted to the Italian situation with different scenarios analyzed. Health system and	Routine vaccination program has a clearly positive impact on chickenpox morbidity. This program would also induce savings from both societal and health system

			societal economic perspective.	perspective in the base case. It is always cost effective.
Coudeville et al. (90)	2005	France Germany	Halloran's transmission model was used for both countries. Cost data derived from previous studies.	Routine vaccination program has a clear positive impact on varicella-related morbidity in both countries. It induces savings in both countries from both societal and third-party payer's perspectives.
Lenne et al. (91)	2006	Spain	Varicella transmission model developed by Halloran adapted to the Spanish context. Two vaccination scenarios were analyzed.	Routine vaccination program has a positive impact on varicella-related morbidity. From societal perspective, it is cost-saving and from Health Care System, it is cost-effective.

Brisson developed another transmission model in 2000, and this model was also a guide for other studies. They considered that Halloran's model focused on incidence and morbidity of varicella due to shifts in the age of infection, however, it did not accurately reflect the epidemiology, and the possible effects of immunization on the epidemiology of zoster were not explored. They developed a mathematical model to simulate transmission of varicella and zoster in developed countries before and after vaccination using Canada as an example. The main questions addressed were: effect of vaccination in healthy children on the overall varicella morbidity, the role of vaccine efficacy on

varicella incidence and morbidity, the effect of vaccination strategies in minimizing incidence and morbidity and the possible impact of vaccination on zoster. The model predicts that the overall (natural and breakthrough) incidence and morbidity of varicella would likely be reduced by mass vaccination of 12-month-old children. Adding a catch-up campaign in the first year for 1-11 year olds seems to be the most effective strategy to reduce varicella incidence and morbidity, though with the possible detrimental effect of increasing the incidence of zoster (64). However, their model includes the variable that the risk of HZ increases if no natural boosters occur following Hope-Simpsons hypothesis and a case control study by Thomas (104). Other studies have analyzed data and created models based on Brisson's mathematical model (Table 6).

Table 6. Studies based on Brisson's mathematical model.

Author	Year	Countries	Model	Results
Brisson et al. (81)	2002	Canada	Deterministic realistic age-structured model to predict impact of vaccination on the incidence of varicella and zoster.	Cost saving and cost-effective. Infant varicella vaccination could result in a short to medium term increase of zoster incidence and cause vaccination to be cost-ineffective under health payer's perspective.
Gidding et al. (105)	2005	Australia	RAS model developed by Brisson. Impact of vaccination with catch-up campaign on the incidence of varicella and zoster.	Infant vaccination reduces incidence of varicella, zoster is expected to increase initially, assuming exposure to varicella boosts immunity to zoster. Accumulated

				morbidity from both predicted to remain above than expected without vaccination for the first 70 years, later health savings will increase.
Brisson et al. (57)	2010	Canada	1-dose vs 2-dose varicella vaccination program.	Second dose will reduce varicella and zoster. Most prevented varicella cases are breakthrough infections.
Van Hoek et al. (97)	2012	UK	Transmission dynamic model to explore various options of VZV vaccine.	A combined policy is cost-effective, influenced by projected benefits that accrue many decades after the start of vaccination. Over shorter time frame, projected rise in the incidence of HZ.
Poletti et al. (106)	2013	Italy Finland UK	Multi-country model of VZV transmission and reactivation to evaluate the possible impact of vaccination.	HZ incidence medium-term will increase in countries rate is low in absence of immunization due to higher force of boosting and minor increase where force of boosting is milder. This incidence depends on presence or absence of factors promoting boost.

Gao et al. (107)	2015	Australia	Impact of discontinuing catch-up vaccination on varicella and zoster incidence and morbidity using transmission dynamic model.	At current vaccine coverage, ceasing program was projected to increase varicella-associated morbidity.

Karhunen's model was a mathematical model of varicella and zoster epidemiology in the Finnish population. The model was based on serological data on varicella infection, case-notification data on zoster, and new knowledge about close contacts relevant to transmission of infection. Their conclusions were that a childhood program against varicella would increase the incidence of zoster by one to more than two thirds in the next 50 years in the >35 years age groups. However, high vaccine coverage and a two-dose program would be very effective in stopping varicella transmission in the population (102).

Other models have been based in Karhunens', such as Guzzeta and Van Lier. Guzzeta's model is based on Hope-Simpson's hypothesis of progressive immunity, and the model is a generalization of Karhunens. The progressive immunity model fits better the age profile of HZ for Finland, Italy, Spain and UK (108). Van Lier's model is a dynamic transmission model, parameterized with Dutch VZV seroprevalence and HZ incidence data, linked to an economic model. They conclude that varicella incidence decreases after introduction of varicella vaccine, while HZ may increase or decrease depending on immune boosting presence (109).

Thus, many models have been developed to study the epidemiology and economical factors of varicella vaccination. Each model is designed in a different way, but all of them conclude that the global incidence of varicella would decrease with the implementation of vaccination and that the incidence of herpes zoster if this occurs is uncertain. Some

of them believe that incidence of herpes zoster would increase during the first years and finally decrease in the long term. Most of the studies affirm universal vaccination is cost-saving from societal point of view and some of them conclude it would also be cost-effective from Health Payers perspective.

2.8.OTHER VACCINES.

Zostavax, a live vaccine against zoster, was developed in 2005. It is an identical strain to the Oka vaccine but 14 times more concentrated.

Proquad is the combination vaccine that contains live attenuated strains of measles, mumps, rubella and varicella (Oka/Merck) and it was authorized for use in USA in 2006. Priorix tetra is GSK's formulation for this tetravalent vaccine and it was launched in Germany also in 2006. Both are licensed in Europe (110).

2.9.STUDY JUSTIFICATION

When this project was started, the Spanish Medicine Agency had just blocked the distribution of the varicella vaccine based on the hypothesis that a partial vaccination coverage as obtained in Spain, between 50 and 60%, could have negative epidemiological effects, such as an increase of cases in the adult population, where the disease is more severe. Also, the duration of immunity was unknown and it could decrease with time, making future adults susceptible to the disease. The third point was the controversial relationship between varicella vaccine and the increase of HZ in the non-vaccinated population.

Therefore, we decided to model the impact of this partial varicella vaccination on the epidemiology of the disease, without taking into account what will happen with HZ in the future, as the result depends directly on including or not in our model the importance of natural boosters to prevent HZ and this, as we have seen, is not clear yet.

Furthermore, the model should include an economic analysis, as the health costs of Spain have largely varied from the time other studies were carried out.

OBJECTIVES AND HYPOTHESIS

3. OBJECTIVES AND HYPOTHESIS

3.1. HYPOTHESIS

When the project started, varicella vaccine was not universal and the vaccine coverage was low. Our hypothesis are:

- Non systematic vaccination of varicella vaccine in Valencian Community decreases the burden of varicella without an increase of cases in adults.
- Universal vaccination against varicella is cost-beneficial in the Valencian Community.

3.2. GENERAL OBJECTIVE

- Estimate the impact of different vaccination strategies in Valencia Community:
    - universal toddler vaccination,
    - risk groups vaccination and in the preadolescent and
    - individual non systematic vaccination in toddlers.

3.3. SPECIFIC OBJECTIVES

- Evaluate the impact of partial varicella coverage on the incidence of varicella in adults.
- Calculate cost-benefit effect of universal vaccination strategy in Valencian Community.
- Calculate cost-benefit effect of risk group and preadolescent vaccination strategy in Valencian Community.
- Calculate cost-benefit effect of individual non systematic and preadolescent strategy in Valencian Community.

METHODS

4. METHODS

4.1.STUDY SETTING

4.1.1. Population studied.

The population studied is that of the Valencian Community. It is one of the 17 Autonomous Regions of Spain. In the year 2012 the total population in the Valencian Community was 5,129,266 inhabitants, and the total population of Spain for the year 2012 was 47,265,321. In the Valencian Community, the rate of birth was 9.9 per 1000 persons per year, and therefore an annual birth cohort in Valencia was approximately 50,780 newborns (Annual Report on the National Health System of Spain 2012) (73).

4.1.2. Demographic data.

The demographic data of the Valencian Community, used in the model is that of the year 2012. From published data we extracted other demographic information that was used for our mathematical model.

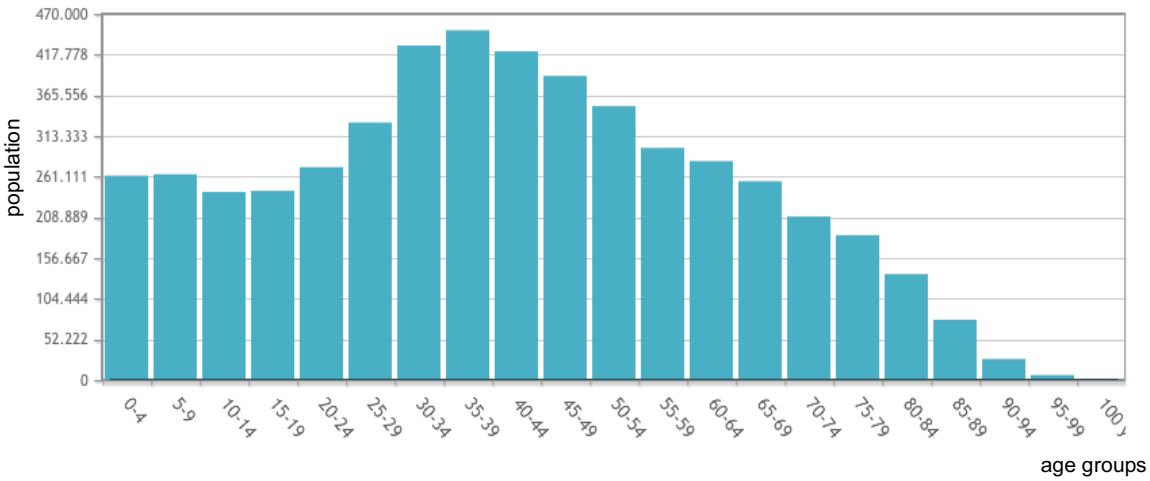

Figure 5. Valencian Community Population Distribution per age groups 2012.

We divide the total population into the age groups described in Table 7 because 0-6 months determine the children maternal immunity (111, 112) and we will use the model to simulate vaccination strategies at 1, 3 and 12 years old. Weekly growth rates have

been calculated using an underlying demographic linear model where we assume that the population of every age group is constant over time.

Table 7. Demographic data of the Valencian Community 2012.

Age group	Population	Death rate	Weekly growth rates
0-6 months	22,945.5	$4.31161 X10^{-7}$	914.885: birth rate
6-12 months	22,945.5	$5.62384 X10^{-8}$	0.0398716
1-3 years (13 to 35m)	103,401	$8.24829 X10^{-8}$	0.0398716
3-12 years	475,759	$1.45095 X10^{-6}$	0.00884774
>12 years	4,504,215	0.00020296	0.00192151

4.1.3. Epidemiology of varicella.

The lifetime risk of acquiring varicella was conservatively estimated to be over 95%, and over 90% of the cases of varicella were children under 10 years (23), with an age dependent incidence.

4.1.4. Incidence of varicella. Seasonal variation.

Due to the lack of reliable data from Spain, the number of infected individuals per week was obtained from a report from Royal College of General Practitioners (113). They averaged the incidence over a period of 10 years without vaccination and reported the weekly incidence depicted in Figure 6.

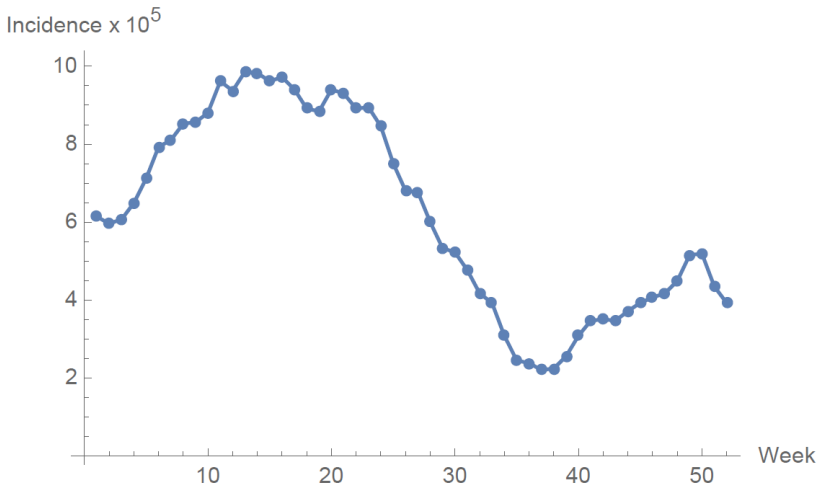

Figure 6. Weekly incidence of varicella infection (cases/100.000)

These figures are very similar to the ones that appeared in the varicella report bulletin of the Valencian Community 2012 (114) (Figure 7), therefore we considered them to be representative of our Community.

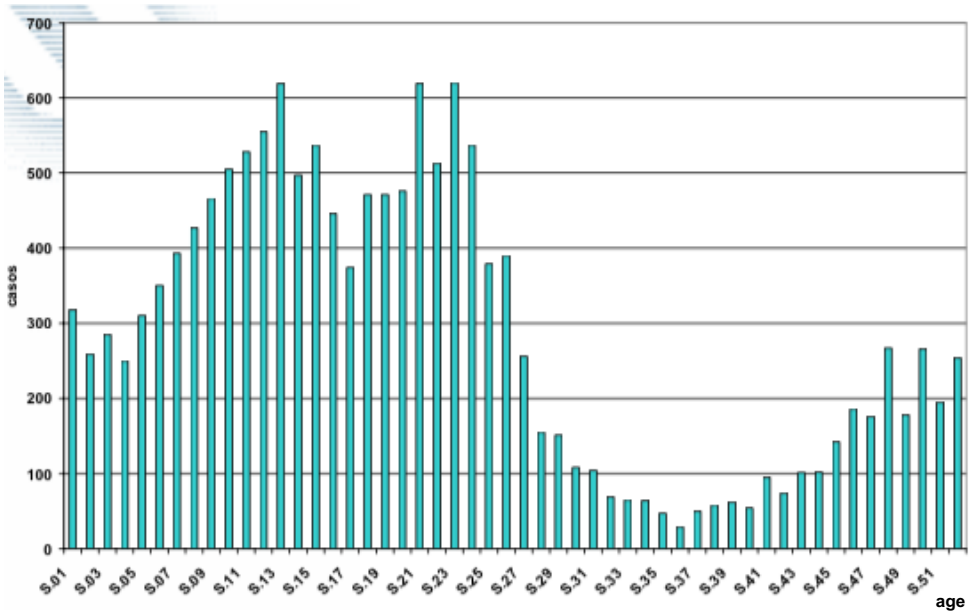

Figure 7. Weekly reported cases in the Valencian Community in 2012 (114).

The epidemiological pattern of the disease is clearly seasonal in our environment, and it varies depending on the week of the year. This is the reason why we considered the incidence of the disease to vary depending on the week, so we included this in our model.

4.1.5. Effectiveness

The effectiveness of the vaccine is high, but varies among studies with different populations and methodologies.

It is clear that a one-dose schedule is not as effective as a two-dose schedule. As the effectiveness of a two-dose schedule has been studied in Spain and the incidence of varicella and specially of breakthrough varicella decreases with this second dose, we will use in our model a two-dose varicella vaccine schedule.

In order to precise the effectiveness of the vaccine, we used the population studied that is the most similar to our population. In Navarra, Spain, they studied the impact of a two-dose varicella vaccination from 2006 to 2012. We used their effectiveness data for our mathematical model (59).

Their conclusions were that in Navarra, Spain, in children aged one to eight years, the incidence of varicella after universal vaccination decreased by 98.5%. In cohorts vaccinated at age 10 to 21 years, the incidence decreased by 93.8% until 16 years of age and 90.1% in patients aged 17 to 21 years. In total, effectiveness of at least one dose of varicella was 96.8% (59). We therefore decided to introduce in our model a vaccine effectiveness of a two-dose schedule of 97%. The effectiveness of 97% is acquired after the first dose and lasts at least de first 5 years after vaccination. The second dose is administered to maintain this effectiveness for a longer period.

4.1.5.1. Adverse events.

Regarding the adverse events produced by the varicella vaccine, we used some of the previous studies that have been developed to analyze this data. Using the Vaccine Adverse Event Reporting System (VAERS), a study showed after 16 million doses, that the rate of adverse events was 67.5 per 100,000 doses and 2.9 severe adverse events per 100,000 doses (71). We based our adverse events numbers on studies developed in Europe, such as the ones published by Coudeville et al., Lieu et al, and Lenne et al (79, 89-91, 103).

In summary, the data we used is that 1% of the vaccinated individuals have adverse events due to varicella vaccine that require medical attention. 95% of these adverse events are attended in primary care, and of the remainder, 5% go to the casualty department of the hospital (91, 115, 116).

4.1.5.2. Loss of effectiveness.

It is not yet established the length of protection of a two dose schedule of the varicella vaccine. In order to be conservative in the estimations, we considered in the sensitivity analysis of the model, that there will be a loss of effectiveness of 1% per year between 15 to 23 years after the vaccine administration.

Thus, the data we used in our model regarding the effectiveness of the varicella vaccine are the following:

- Vaccine effectiveness of a two-dose schedule: 97%.
- The effectiveness of 97% is acquired after the first dose and lasts at least the first 5 years after vaccination. The second dose is administered to maintain this effectiveness for a longer period.
- 1% of the vaccinated individuals have adverse events that requires medical attention, 95% of them attended in primary care and the remainder seek attendance in the casualty department of the hospital.
- A partial loss in the effectiveness of 1% per year 15 to 23 years after the vaccine administration.

Table 8. Epidemiological data for our model.

VARIABLE	BASE CASE
Demographic data Valencian Comm.	
- Total population	5,129,266
- Annual birth cohort	50,780

- Mortality rates	See table 7
Weekly incidence	Variable. Figure 6.
Efficacy of a 2-dose schedule	97%
Loss of effectiveness	
- 15 to 23 years after vaccination	1% per year
Adverse events	
- Require medical attention	1%
- Attend primary care	95% of 1%
- Casualty department	5% of 1%
Varicella characteristics	
- Duration of the latent period	14 days
- Duration of infectious period	7 days
- Mean duration of protection through maternal antibodies	180 days
Vaccinees at 1 that revaccinate at 3	100%

4.1.6. Economic.

Economic data were introduced in the dynamic model to assess the pharmacoeconomic impact of the vaccine.

The cost of the vaccine considered in the model:

- The cost of the vaccine for the families was 67.91€ (2014; Spanish Medicine Agency)
- The cost of the vaccine for the health system was 29.07 € (bought under a tender).

As in every mathematical economic model, the cost of vaccine handling, cold chain and purchase must be added to the price of the vaccine. It is generally considered a 10% of the official price of the vaccine (29.07 + 0.1%) (78).

In Spain, childhood vaccinations are usually performed by a nurse who works for the health system. To determine the costs of vaccine administration, we assumed that the time required for the on-shot vaccination was 5 minutes. As nurses in Spain are paid an average of 22€ per hour, the total cost of the vaccine administration would be 1.85€. This data is obtained from a study in Valencia, where the time used to deliver 455 vaccinations was analyzed (117).

The conservative standard annual discount rate of 3% was applied in this model, however with the present economic situation, the tendency is to consider the discount rate of 0% or even as a negative figure as there is no inflation (118, 119).

We assumed that all the 1-year-old vaccinated children were also vaccinated when they were 3 years old, as this is what usually happens in Spain with the rest of the vaccines, and is also expected to occur with the varicella vaccine (120).

The data for the economic model have been obtained from (91), updates from (91) and (121). All these data have been summarized in Table 9.

Table 9. Data for the economic model ((91), updates from (91) and (121))

Medical consultation cost	*Age groups*	*% cases that need consultation*	*Average consultations per case*	*Cost per consultation*
Payer:	≤14 y.o.	90%	1.54	49 €
	14-16 y.o.	100%	2	28 €
	≥16 y.o.	100%	2	28 €

Casualty consultation cost	*Age groups*	*% cases that need consultation*	*Cost per consultation*
Payer:	≤14 y.o.	5%	187.61 €
	14-16 y.o.	5%	187.61 €
	≥16 y.o.	5%	187.61 €

Hospitalisation cost	*Age groups*	*% cases that need hospitalisation*	*Average hospitalization days*	*Cost per hospitalization day*
Payer:	≤14 y.o.	0.23%	6	512.55 €
	14-16 y.o.	1.36%	7	273.09 €
	≥16 y.o.	1.36%	7	273.09 €

Pharmaceutical prescriptions	*Age groups*	*% cases with prescriptions*	*Average cost*
Payer:	≤14 y.o.	90%	15.11 €
	14-16 y.o.	100%	22.55 €

	≥16 y.o.	100%	22.55 €

OTC medications	*Age groups*	*% cases that use OTC*	*Average cost*
Payer:	≤14 y.o.	23%	3.56 €
	14-16 y.o.	23%	3.56 €
	≥16 y.o.	23%	3.56 €

Work loss	*Age groups*	*Days lost per case*	*Economically active population rate*	*Cost per day*
Payer:	≤14 y.o.	0.97 (parents)	-	108.45 €
	14-16 y.o.	0.97(parents)	-	108.45 €
	≥16 y.o.	10.5	64.1%	108.45 €

The costs that were evaluated and are included in model are as follows:

- Payers perspective: The payer is considered to be the Regional Governement, called “Conselleria de Sanitat”, this means, what is paid by the health system in Valencia. Includes vaccination paid by NHS.
- Indirect cost: includes every costs that are not paid by health system, sanitary costs such as vaccines paid by parents, and other non sanitary cost such as work loss by parents or varicella cases in adults.
- Vaccination cost afforded by the parents: it is included in the indirect costs; it is the part of these costs representing what parents pay for the vaccine.
- Total cost: payers perspective (health system) cost + indirect cost.

4.2. MATHEMATICAL MODEL

Inspired by the success of network models in the simulation of other infectious diseases in our research group (122) we considered the network method to implement a simulation of the evolution of the varicella disease.

However, the simulation of the network model showed complicated evolution patterns reminiscent of chaotic behavior. This should require a study in itself and, as the objective of this work was to simulate the seasonal pattern found in this disease, we abandoned the network method and opted for difference equations with variable coefficients.

4.2.1. Basic model.

The basic model was a $S - L_1 - L_2 - I - R - L_1$, i.e., a Susceptible-Infected-Recovered or SIR model but with two intermediate latent stages and the possibility to become latent after being recovered. The diagram for this compartmental model is shown in Figure 8:

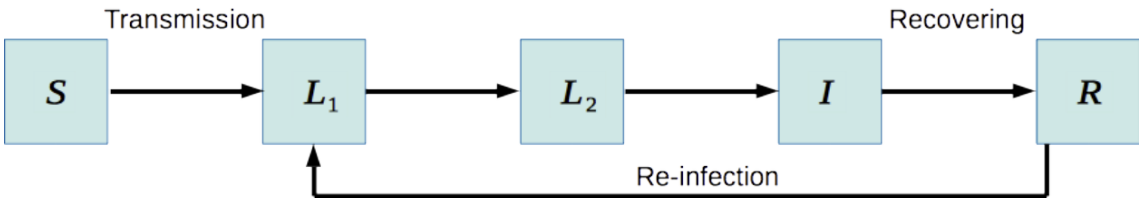

Figure 8. Compartmental model for Varicella Epidemiology, where S = susceptible, L1 = Latent of 1st= latent first week, L2 = Latent of 2nd= latent second week, I = infected, and R = recovered.

Every individual has an assigned state with respect to the virus:

- Immune: a child under six months of age who is immune to the disease as a consequence of maternal protection. High levels of IgG against VZV have been detected in children during the first months of life (111, 112).
- Susceptible: a healthy individual who could become infected.

- Latent first week: an infected individual during the first week. In this state, the individual cannot be the source of contagion. This is an incubation period.
- Latent second week: the same as above but the individual becomes contagious.
- Infectious: After the two latent states the infected individual develops the disease and the characteristic vesicles and becomes extremely contagious. This state lasts another week.
- Recovered: These individuals have developed the disease and, after clearing the infection, they have almost total lifelong immunity forever. Reinfection may occur in some cases but it is very rare, about 10%.

Ours is also an age-group model in which we take into account the following age-groups:

- G(1): 0-6 months.
- G(2): 6-12 months.
- G(3): 1-3 years.
- G(4): 3-12 years.
- G(5): older than 12 years.

As we are interested in a model with all the age groups with constant population the death rate for age-group G(5) was chosen accordingly.

The structure of the compartmental model we propose is given below in Figure 9.

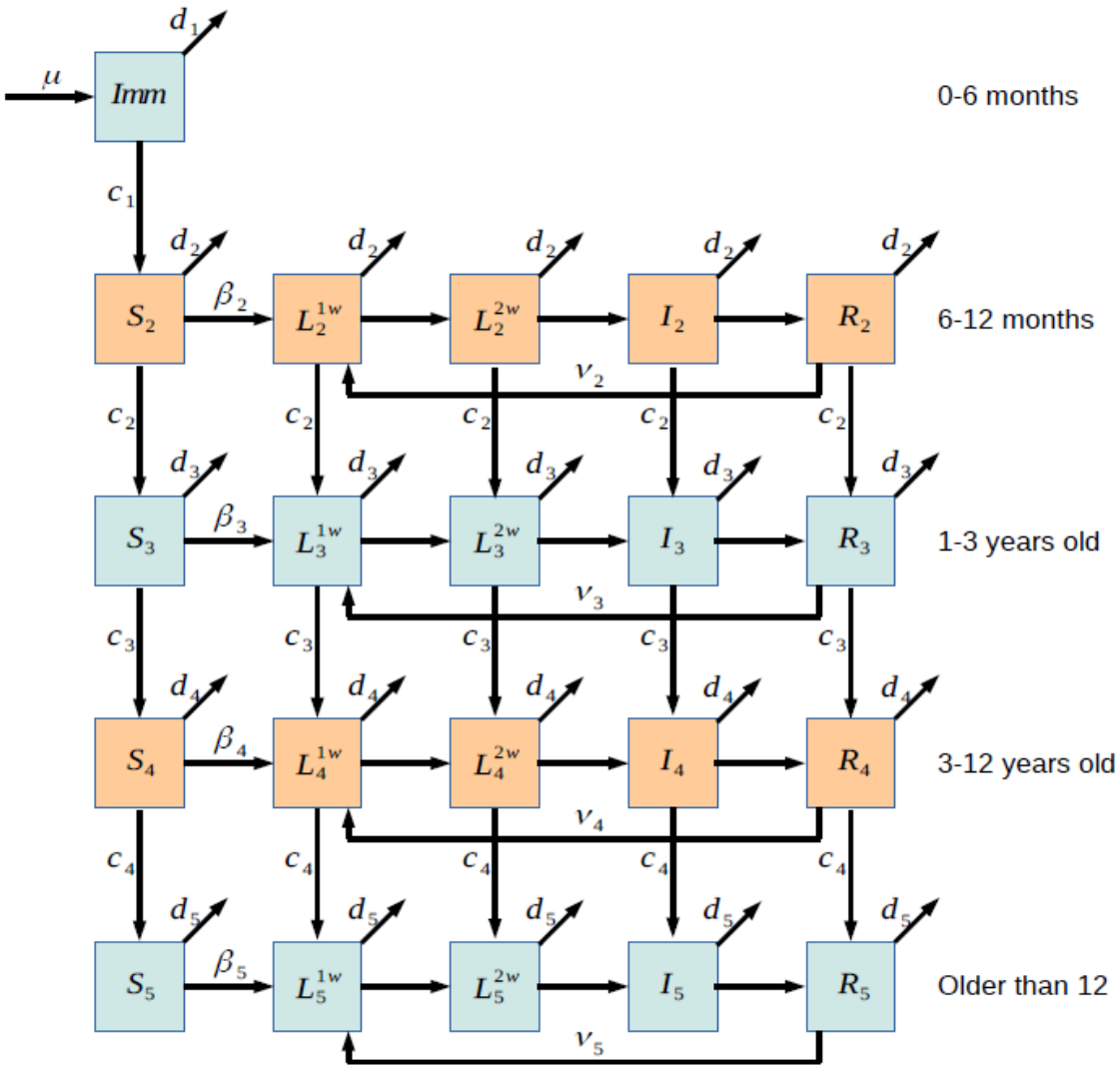

Figure 9. Age-structured compartmental model for varicella infection

Variables of the model:

- d_i, *i=1,..,5* are the death rates,
- μ is the birth rate,
- B_i, *i=2,..,5* are the infection rates,
- v_i, *i=2,..,5* are the reinfection rates and
- c_i , *i=1,…,4* are the transition rates between age-groups chosen in such a way that the population of the age groups remain constant.
- Imm = immune children under six months,
- S_i = susceptible,
- L_i^{1w} = latents of 1st week,

- L_i^{2w} = latents 2nd week,
- I_i = infected,
- R_i = recovered.

Our age-structure model includes a system of difference equations where we considered the transmission depending on the age group, and on the week of the year. During the calibration process, we noted that the typical approaches using transmission forcing terms (122, 123) did not work properly, so we defined a procedure to determine the weekly transmission value that explained the epidemiology, and therefore we considered that in Figure 10.

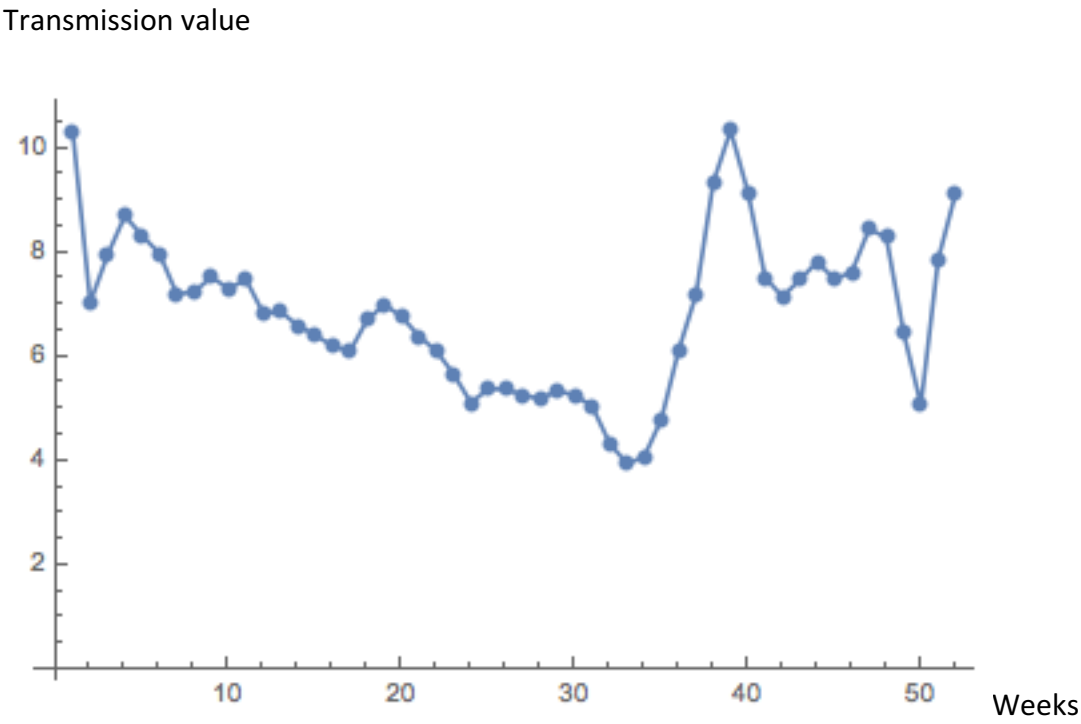

Figure 10. Varicella transmission values per week.

The transmission values for the age groups are proportional to the transmission per week, with different rates of proportionality. It is worth to note that although the varicella pattern is seasonal (Figure 6, 7), the varicella transmission rate is not.

This approach permitted a better calibration of the models parameters, and allowed a more accurate model output.

After the calibration of the model, different vaccination strategies were included in the model.

Red lines determine the transitions for vaccinated individuals. On one hand, 1-year-old susceptible individuals are vaccinated and transit to box V_3. Here we were assuming that all children vaccinated at 1 year of age, would be vaccinated again at 3 years of age as we mentioned before. On the other hand, 12-year-old susceptible individuals are vaccinated and transit to box V_5. In this model we considered that, once a child is vaccinated at 1 and 3 years of age or at 12 years of age, they get a permanent immunization. Later, we performed a sensitivity analysis assuming an effectiveness loss of 1% per year, during 7 years, and starting about 15 years after the complete vaccine schedule.

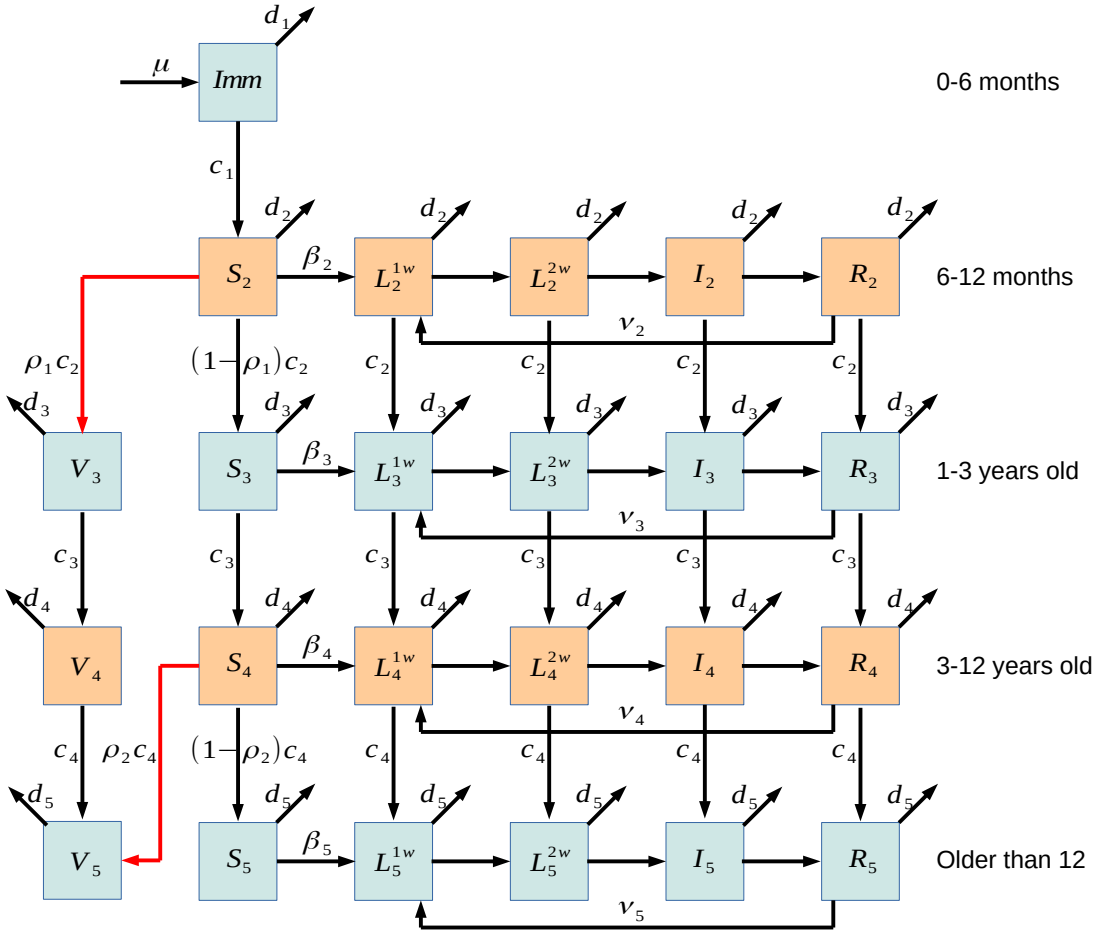

Figure 11. Age-structured compartmental model for varicella infection with vaccination where V are vaccinated subjects.

The only new parameters respect to the ones described in Figure 9 are ρ_1 and ρ_2, and they determine the vaccination rates. Finally, V_i = vaccinated, *i=3, 4, 5*.

As the main problem with the free vaccination that achieved partial coverage was the potential shift of the disease to older age groups, we assessed, the number of infected individuals per year in the following 50 years with coverages ranging from 50-90% in children of 1 and 3 years old and a constant coverage of 90% in susceptible children of 12 years of age.

4.3.VACCINATION PROGRAMS

Different vaccination strategies were analyzed:

1. A ***base case consisting of no vaccination*** that reflects the varicella epidemiology if no vaccine were licensed or used.
2. 12-year vaccination: Vaccination of high risk children and those reaching 12 years without history of the disease or the vaccine with a vaccine coverage ranging from 80 to 100%. The health system pays for these vaccines. This was the program in the Valencian Community when this study started.
3. Universal vaccination: with a two dose vaccination strategy, at 12 months and at 3 years of age with a vaccine coverage of 96%. Besides, subjects reaching 12 years old without history of the disease or the vaccine would be vaccinated with a 90% coverage. The health system pays for the costs. This is the present schedule in Valencia.
4. Individual vaccination: apart from the vaccination program at 12 years of age (coverage 90%), parents paid for the vaccine of their children at 1 and 3 years old with coverage ranging from 10% to 90%. This was the situation before 2014.

In each case the model simulates 50 years from the time the vaccine program is implemented.

4.4. SENSITIVITY ANALYSIS

We performed different sensitivity analysis:

1. Immunization loss of 1% per year, during 7 years, starting about 15 years after the complete schedule (at 3 years old). For those vaccinated at the age of 12 years we considered that there was no loss of effectiveness.
2. Assumption of an effectiveness loss of 1% per year.
3. Different effectiveness loss of 0, 2.5 and 5% in 10 years.

RESULTS

5. RESULTS

5.1. MODEL CALIBRATION. EPIDEMIOLOGY OF VARICELLA IN VALENCIA.

To create our epidemiological pattern, the data in figure 7, that represented the varicella reported cases in the study population, was replicated for 4 years. The model was calibrated and adjusted to fit a scaled number of infections per week, in the replicated 4 years.

5.1.1. Week variability.

The infection rate is an unknown variable, and is a key parameter of the model, therefore, we constructed a varying estimator that depended on the week of the year, as described before. Additionally, a scale factor was used to obtain the number of cases for our population from the reported cases.

Figure 12 shows the data given by the model compared with actual data obtained from epidemiological studies. This fitting is unusually good for this kind of model, because it reconstructs both the global and local extremes: maxima and minima prevalence.

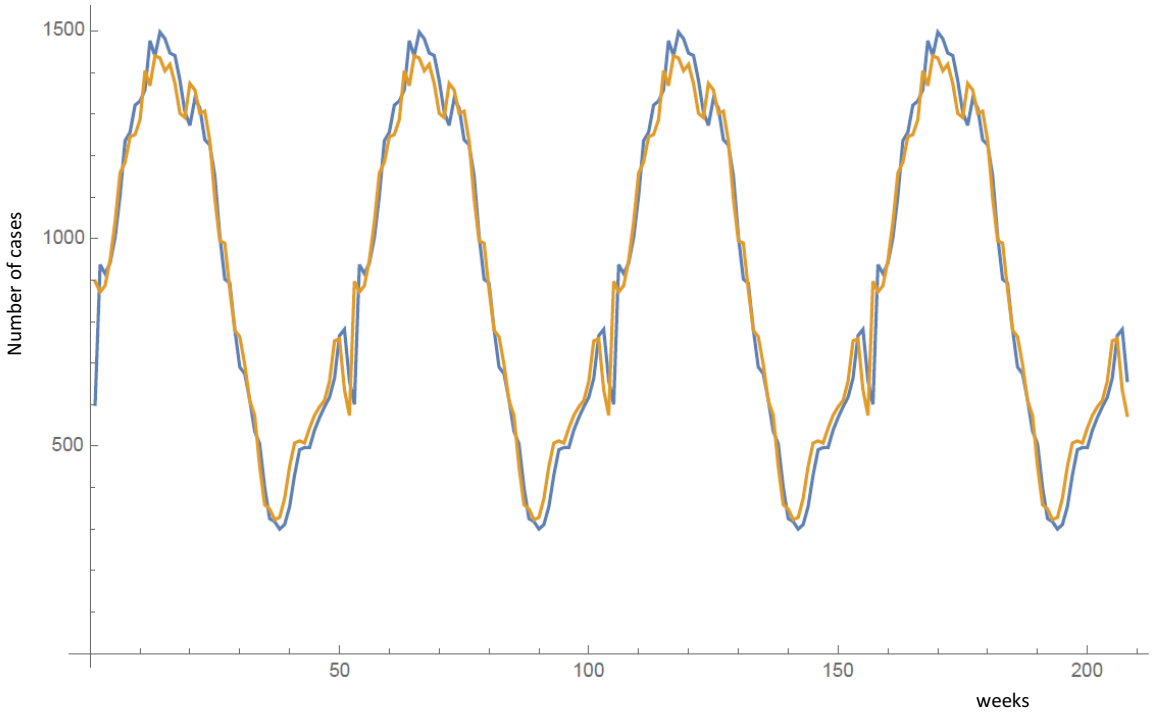

Figure 12: Number of weekly cases of varicella for four years in the Valencian Community as a result of the fitting of the mathematical model (blue line) and the replicated averaged and scaled data for UK (orange line).

5.1.2. Varicella distribution per age groups.

The model was also calibrated to obtain percentages of varicella cases per age group in Spain according to the reported epidemiology by Peña-Rey et al. (24).

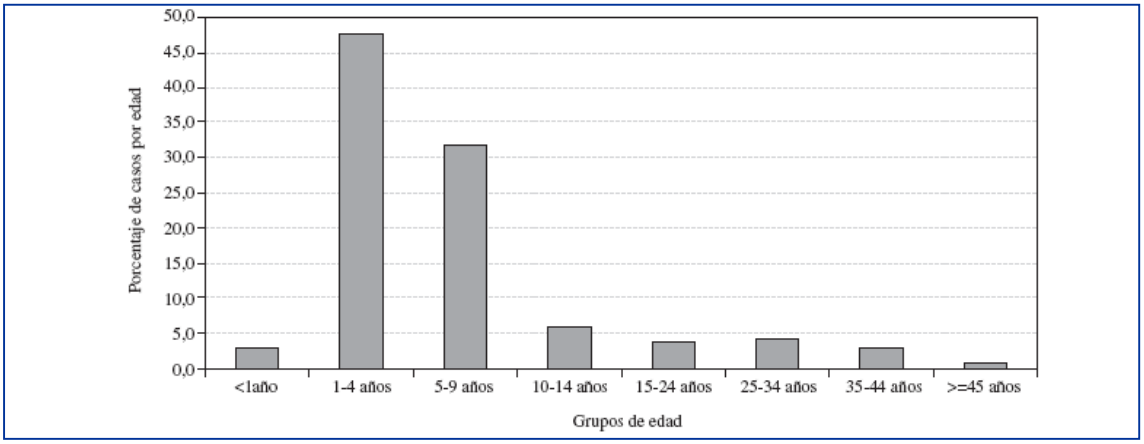

Figure 13. Varicella Epidemiology per age groups in Spain in 2007 (24).

The model gives very similar percentages to those published for each age group (Table 10). Minor differences were expected as our model was designed to mimic different age groups, more related to vaccination programs.

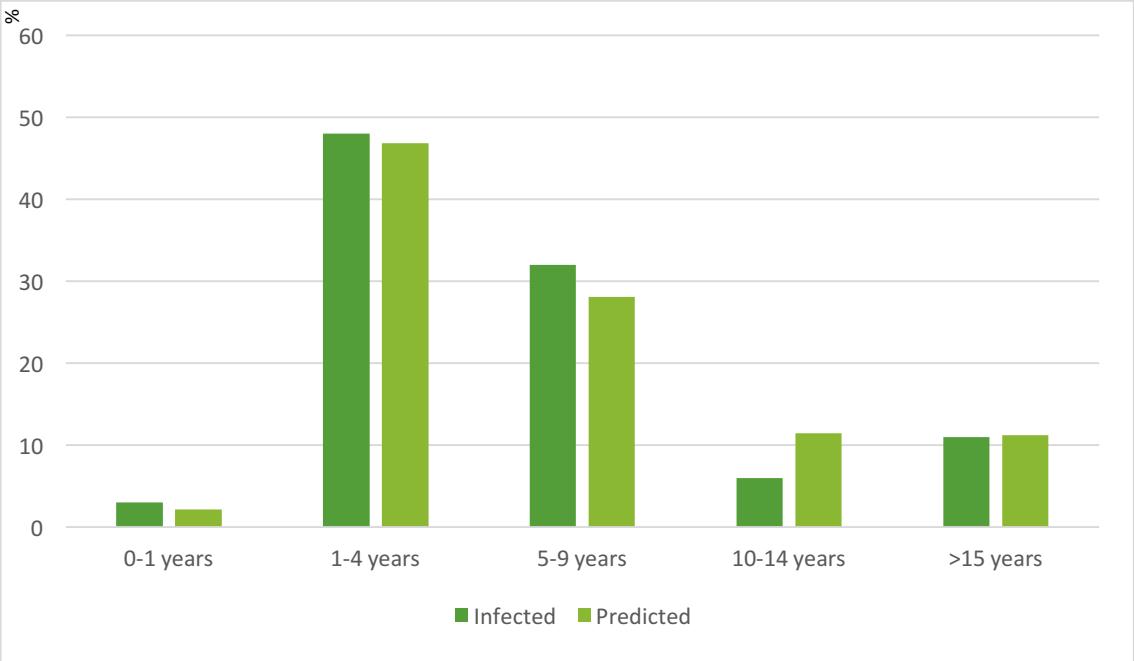

Figure 14: Actual and predicted percentage of varicella infections per age group.

Table 10: Actual and predicted percentage of varicella infections per age group.

Age group (in years)	Actual: % infected	Model: % of predicted infected
0-1	3	2.2
1-4	48	46.9
5-9	32	28.1
10-14	6	11.5
15+	11	11.2

That means that the predicted number of varicella cases per age group in the Valencia Region of Spain is that of the expected. (Figure 15)

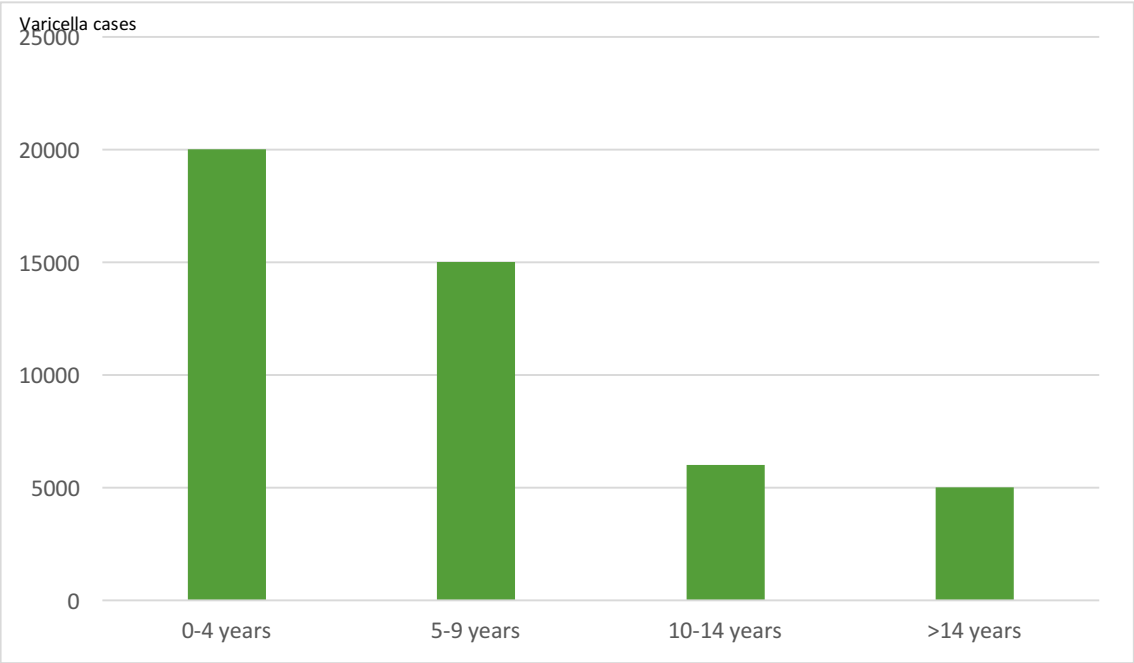

Figure 15. Number of model predicted varicella cases per age group.

5.1.3. Other data.

The model provides the following data that are consistent with other data appearing in the literature:

- 98.2 % of the birth cohort is infected every year.
- There is an average of 15 infectious individuals every 10,000.
- Around 54.8 % of the children are infected before they reach 5 years of age.
- Susceptible individuals are 7.3 % of the total population.
- 6200 children are susceptible when they reach age 12 years (around 13% of the cohort).
- Recovered account for 92.7 % of the total population.
- Around 1,300 persons of all ages are re-infected each year.

5.2. ESTIMATED IMPACT OF VARICELLA VACCINATION

5.2.1. Impact of different vaccination programs in the epidemiology of varicella.

Figures 16-18 depict the estimated impact of different vaccination strategies on the number of cases. The base-case reflects the epidemiology with no vaccination. All other strategies consider different strategies in the toddler and always a vaccination program at 12 years of age of those without history of vaccination or having suffered a varicella.

5.2.1.1. Number of varicella cases in all ages, with different vaccination coverages.

The base case estimates about 50,000 infected cases per year, similar to the birth cohort. With a vaccine program at 12 years, there is a small decrease on the number of total cases, which represent the varicella cases averted in adults.

The moment the vaccination to toddlers starts, there is an important decrease in the total number of varicella cases, which is related to vaccine coverage. When vaccine coverage reaches 90%, the number of cases almost disappeared. In general, the number of varicella averted is always higher than the vaccine coverage, and this is due to different degrees of herd immunity.

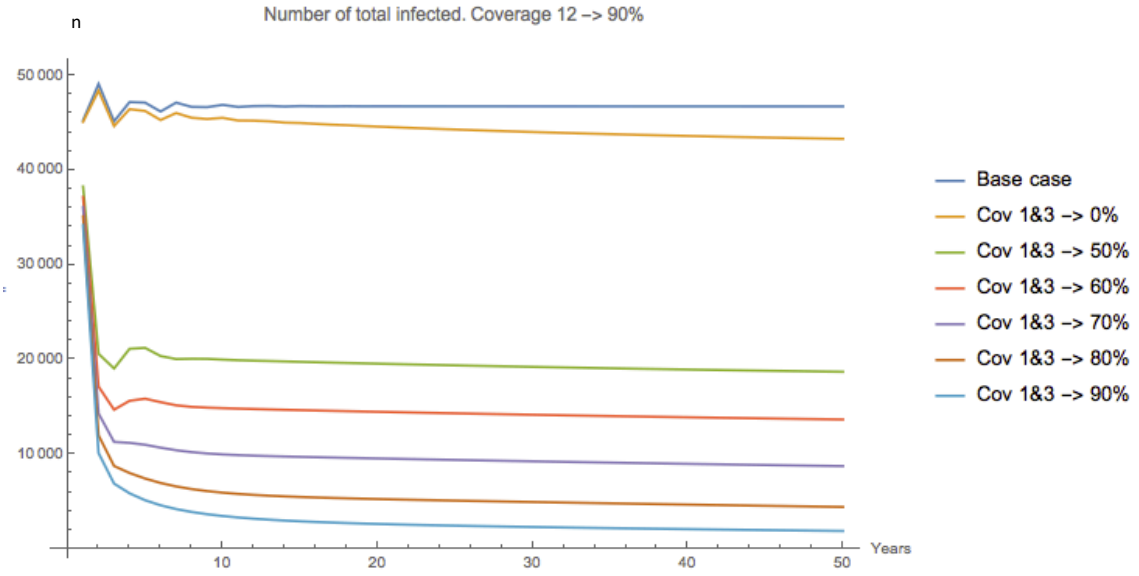

Figure 16: Number of the total infected individuals per year, in each of the following 50 years, with different coverages and no vaccination (case base).

5.2.1.2. Number of cases in children younger than 12 years of age with different vaccination coverages.

The number of infected children younger than 12 years of age decreases when the vaccination in toddlers starts. In the case where only the catch up vaccinations takes place, the decrease of the infected younger than 12 is very low compared to the base case, as the herd immunity is nearly absent.

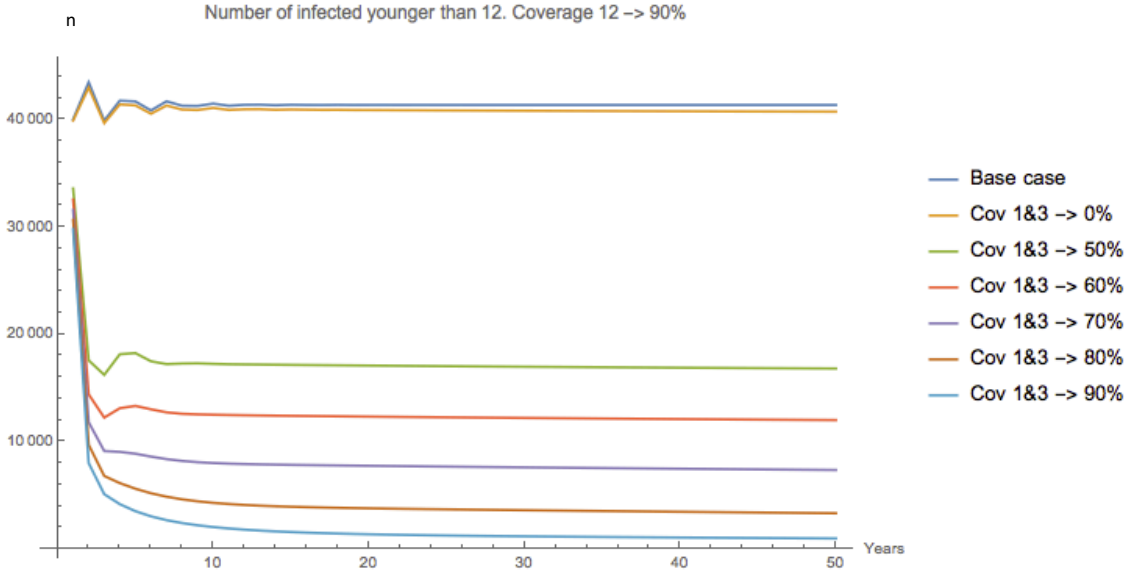

Figure 17: Number of children under 12 years old infected each year in the next 50 years. Different varicella vaccine coverages.

5.2.1.3. Number of cases in subjects older than 12 years of age with different vaccination coverages.

The disease is more severe in adults. Any shift of the disease to older ages should be anticipated.

The model predicts a decrease in the total number of older than 12 years infected with every vaccine coverage. With the vaccine program at 12 years of age, the number of infected adults halves. Due to the herd immunity, the number of infected adults decreases in any case when toddlers are vaccinated.

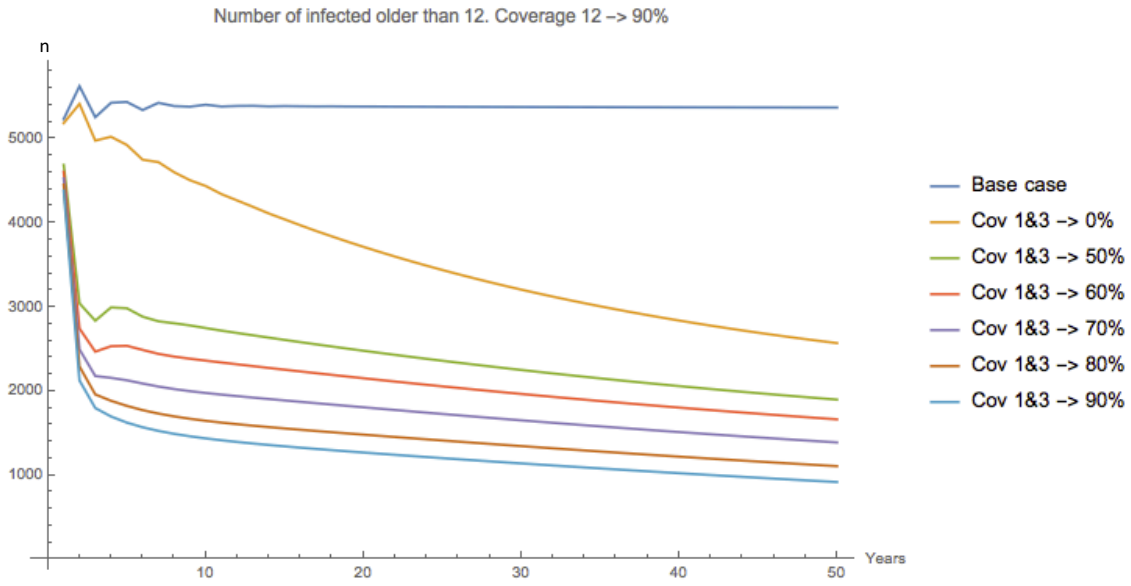

Figure 18: Number of infected individuals older than 12 years old per year, in the following 50 years, with different vaccine coverages.

5.2.1.4. Number of susceptible children reaching 12 years, candidates for vaccination program.

Due to herd immunity it could be expected that the number of subjects reaching 12 years of age being susceptible increases. That would have impact on the vaccination program.

Figure 19 shows the number of subjects susceptible to varicella reaching 12 years of age. This number is higher when low vaccine coverages are reached than in the base case, as there is less virus circulating and less children become infected. When vaccination coverage in toddlers reach 90% to the number of susceptible 12 year-olds is lower than in the base case, i.e. without vaccination in toddlers

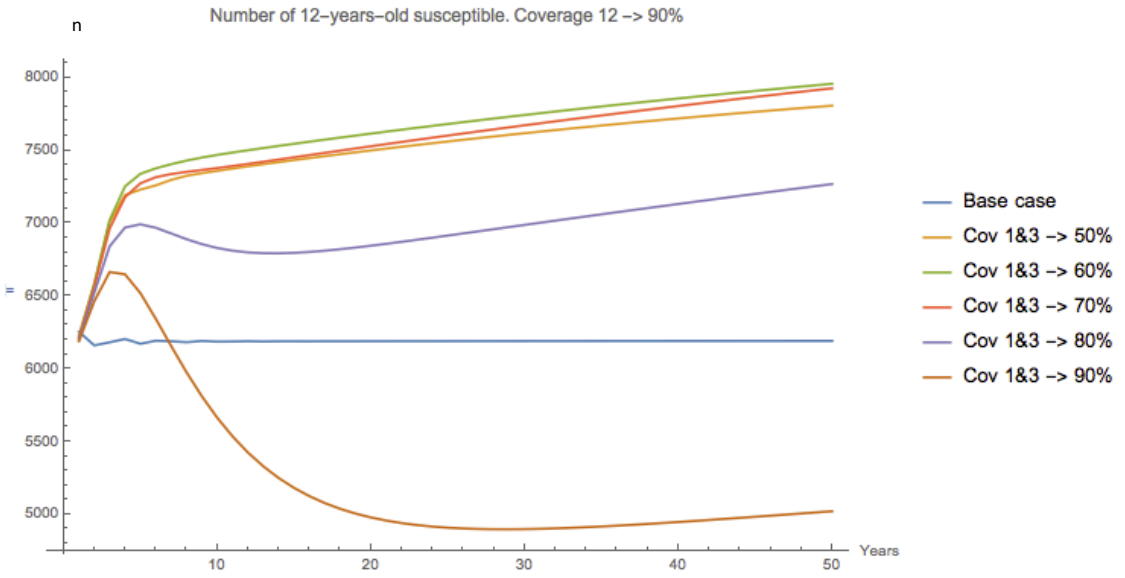

Figure 19: Number of susceptible 12-years-old children per year in following 50 years, with different vaccination coverages in toddlers.

The number of susceptible individuals at 3 years that are also susceptible at 12 years represents the number of unvaccinated subjects that are not infected during childhood. For a coverage of 0%, the number of 3-year-old children that reach the age of 12 being susceptible is about 12%, as most of the children will acquire the disease during childhood. This resembles data published before vaccine licensure.

When the vaccine in toddlers starts, the number of susceptible individuals at 3 years of age decreases, but there is less virus circulating, so less children will be infected, and therefore the number of susceptible individuals at 3 that reach the age of 12 being susceptible is higher when vaccination coverage reaches 90% over 80% of the unvaccinated will reach the age of 12 susceptible.

When a vaccine coverage of 70% is reached, there is a change in the evolution and herd immunity effect produces a remarkable increase in the percentage of susceptible individuals, as they are not infected while they are younger. These non-vaccinated susceptible are better protected against infection because of the herd immunity. This means that, even though the number of susceptible individuals that reach the age of 3 and therefore 12 is much lower, the difference between them is very low because there

is very few virus circulating, and therefore the percentage of susceptible individuals at 3 that reach 12 being susceptible is very high.

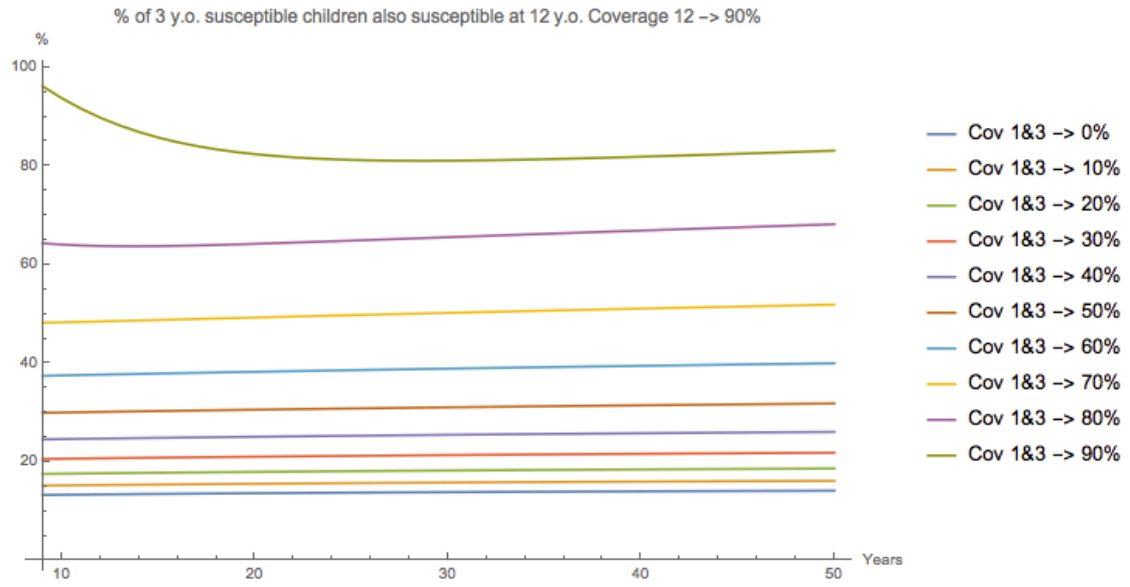

Figure 20: Percentage of 3-years-old susceptible that are susceptible at 12-years-old.

5.2.1.5. Transition from the partial vaccination to the universal vaccination strategy.

During the period of development of this thesis, the vaccination program in Spain changed to universal vaccination at 12 and 3 years, therefore we had to adapt our model to show the impact of this change in the vaccination schedule. Therefore, we considered that after initial partial vaccination we changed the schedule to vaccination at 1 and 3 years of age maintaining the catch up at 12 years.

- We consider a 50% coverage for the toddler vaccination and a 90% coverage for the 12-year-old susceptible vaccination.
- 25 years after the vaccination starts, the vaccination strategy changes to a universal 1 and 3-year-old vaccination, reaching a 95% coverage.

Under this new strategy, we could consider 3 potential scenarios:

1. When universal vaccination starts, vaccination of susceptible 12 year olds is withdrawn.

2. When universal vaccination starts, vaccination of susceptible 12 year olds is maintained for 11 years, until the first toddler vaccinated turns 12 years old, and after this, the catch up is withdrawn.
3. Catch up vaccination of susceptible 12 year olds is maintained forever.

Figure 21 shows the total number of infected individuals every year, starting with the vaccination strategy. Note at 25 years the incidence decreases because universal vaccination starts. There seems to be no important differences, however, this is caused by the graph scale.

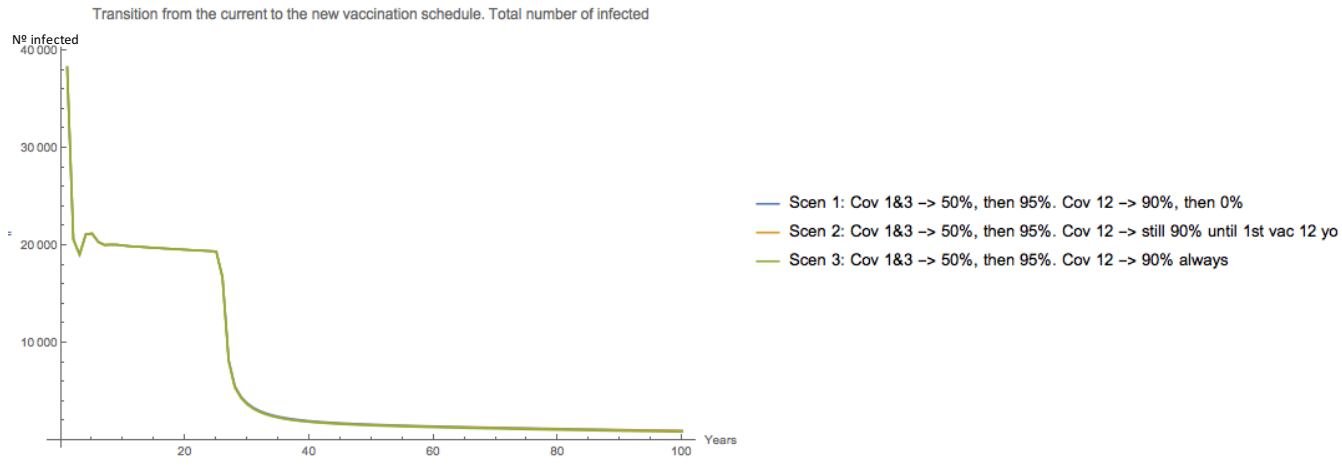

Figure 21. Transition from the partial vaccination to the universal vaccination strategy in year 25. Total number of infected for 100 years after introduction of the vaccine. For the first 25 years, the vaccination strategy is a vaccination of toddlers with a 50% coverage and a catch up at 12 years of age with a 90% coverage. In year 25, 3 different vaccination strategies, all of them with universal vaccination at 1 and 3 years with a vaccination coverage of 95%. The catch up at 12 years varies in the different strategies: withdrawn, maintained for 11 years or maintained forever.

To be more accurate in the differences, we calculated the difference of total infected between scenario 1, where catch up vaccination is withdrawn when universal vaccination starts in year 25, and scenario 2, where it is maintained for 11 more years, and the difference of total infected between scenario 1 and scenario 3, where catch up is maintained forever.

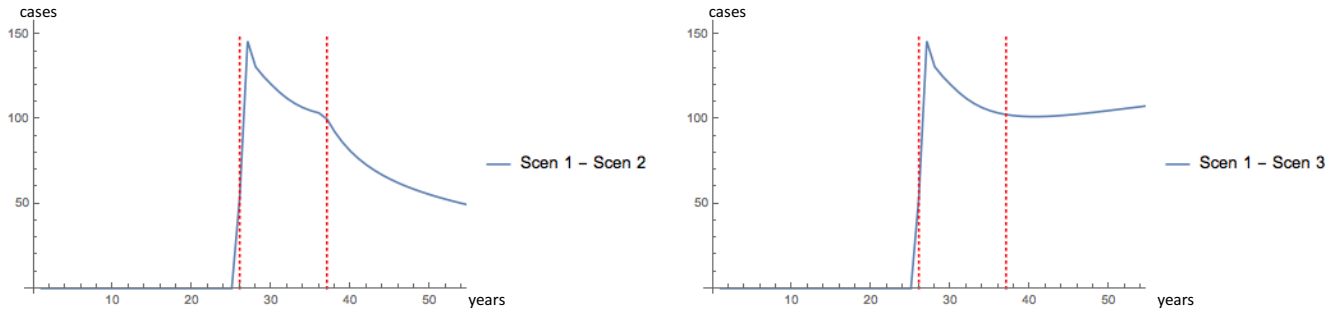

Figure 22. Number of varicella cases averted compared with withdrawal of vaccination at 12 years of age when universal vaccination starts. A) vaccination at 12 years of age is maintained for the following 11 years after initiation of universal vaccination. B) Vaccination at 12 years is maintained forever.

The highest peak in both graphs corresponds with the vaccination strategy change and the introduction of universal vaccination, represented by the first red dotted vertical line.

In graph A we can see the difference on number of varicella cases when the vaccine at 12 years is withdrawn after universal vaccination starts (scenario 1) and when it is maintained for 11 years (scenario 2). After the start of universal vaccination, the difference of infected individuals is about 150 adult cases per year, and after 11 years, when it is withdrawn, the difference decreases to 50 adult cases per year, but a difference is always maintained. This means, the catch up helps maintain the low incidence of infected individuals, especially older aged people, and once it is withdrawn there are more infected individuals, but always less infected individuals if it is withdrawn after 11 years, and not when universal vaccination starts.

In graph B, comparing withdrawal after universal vaccination starts (scenario 1) and maintaining the 12-year-old vaccine forever (scenario 3), the difference of 150 cases in adults is maintained in time. This means, if the catch up is withdrawn when the universal vaccination starts, there is going to be a higher number of infected individuals than if it is maintained for 11 years or forever.

If 12-year-old vaccination was withdrawn, subjects per year would be infected of varicella, that means that during the 11-year transition, our model predicts that there would be 1328 - 1330 infections specially in adults over 12 years of age.

After withdrawal of the catch up at 12 years, 11 years after universal vaccination, there would be a higher number of cases of adults than if the catch up is maintained, representing the number of unvaccinated toddlers that reach adulthood.

In figure 23, it seems to be very little difference because of the scale of the graph.

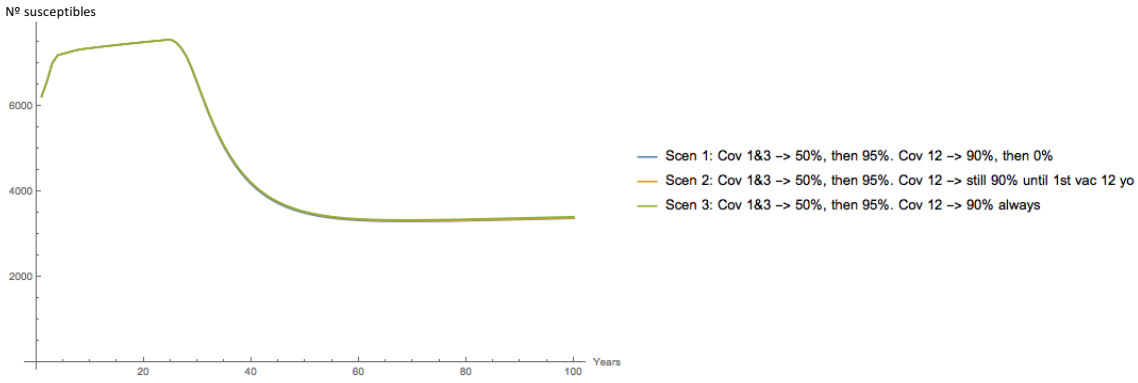

Figure 23. Total number of susceptible individuals reaching the age of 12, considering the vaccination strategies mentioned before.

When universal vaccination starts 25 years after the vaccine is introduced, the number of susceptible individuals that reach the age of 12 decreases, about 10 years later, when the universal vaccination cohort reaches age 12. Afterwards, the number of susceptible individuals remains stable.

In summary, the total number of infected subjects older than 12 years over time, considering the 3 different scenarios is depicted in Figure 24.

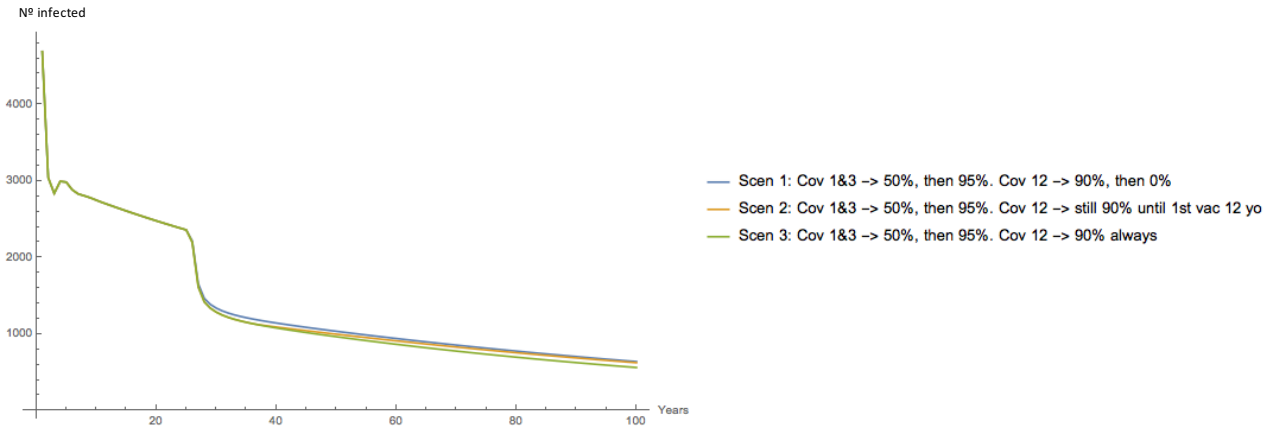

Figure 24. Total number of infected individuals older than 12 years of age in the 3 different scenarios.

The total number of older subjects infected is always smaller after the introduction of the different scenarios.

5.2.2. Sensitivity analysis.

5.2.2.1. Sensitivity analysis assuming a loss of immunity of 1% per year.

5.2.2.1.1. Total varicella cases number assuming a loss of immunity of 1% per year.

The total number of infected at any age (Figure 25), when assumed a loss of immunity of 1% per year starting 15 years after the complete schedule at 3 years, is higher over time than compared to results shown in Figure 16. But even in this case, there is always a significant difference of infected averted than in the base case.

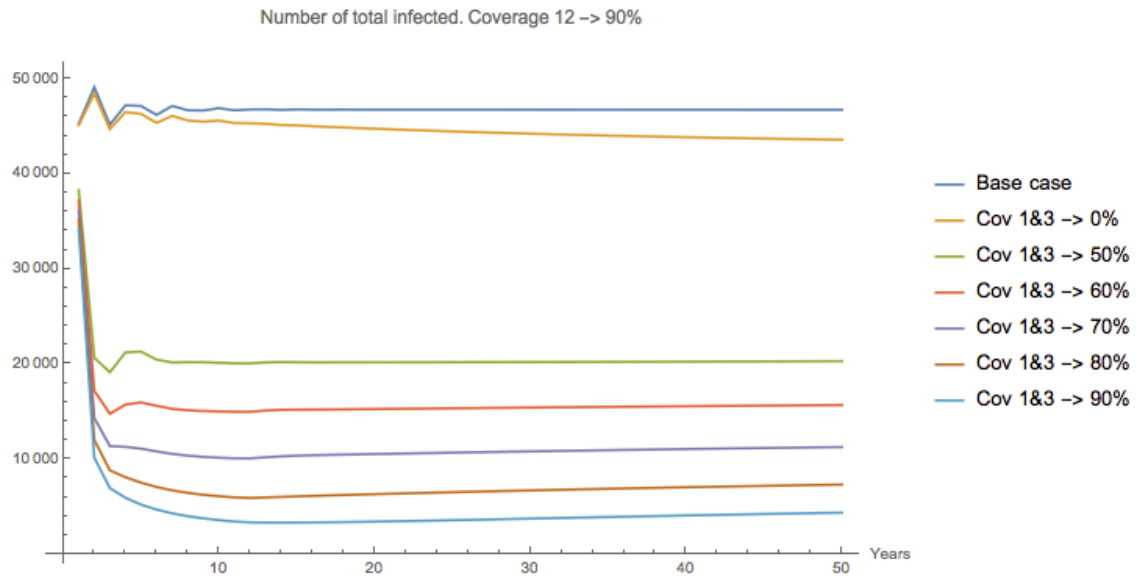

Figure 25: Number of infected individuals with different vaccination strategies assuming that the children vaccinated at 1 and 3 years of age lose the immunity provided by the vaccine at rate 1% per year.

5.2.2.1.2. Number of cases older than 12 years assuming a loss of immunity of 1% per year.

The estimated number of subjects infected older than 12 years is shown in Figure 26. It is in these ages where the effect of loss of immunity is more dramatic. There is a greater increase in the total number of infected individuals as time goes on and coverage increases. But even so, the number of cases in older subjects is always lower than in the base-case. In this case, after 50 years the number of cases in adults is similar to the program where only 12 years of age subjects are vaccinated.

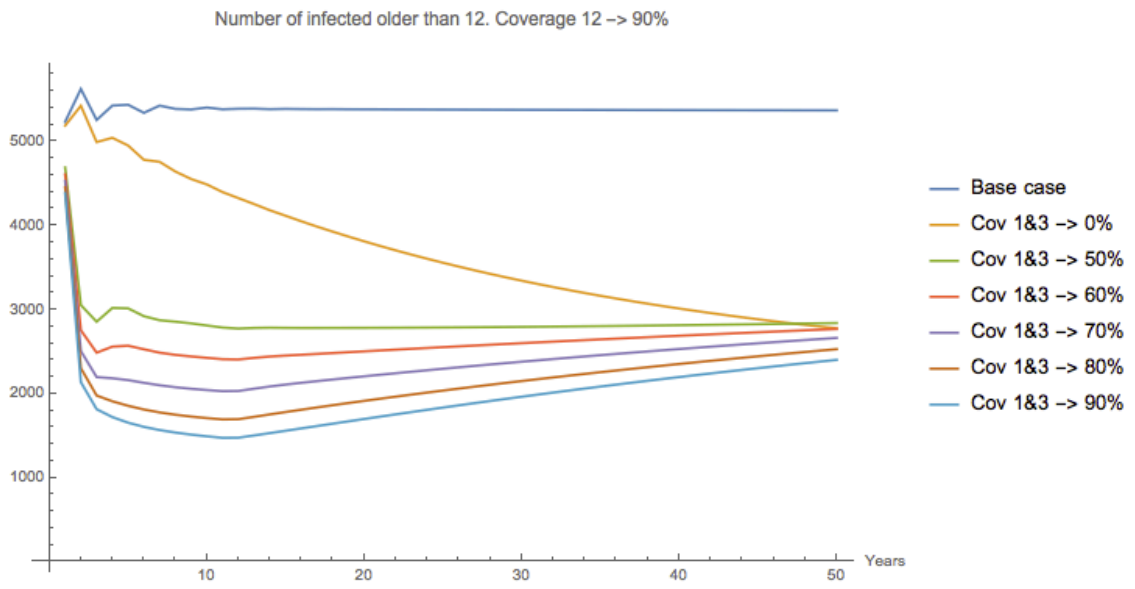

Figure 26: Number of infected individuals older than 12 years old in several vaccination strategies assuming that the children vaccinated at 1 and 3 years of age lose the immunity provided by the vaccine at rate 1% per year.

5.2.2.2. Sensitivity analysis assuming a loss of vaccine effectiveness.

5.2.2.2.1. Total number of infected considering effectiveness loss of the vaccine.

It is not clear whether the effectiveness of the vaccine varies after a two dose schedule. In order to be conservative in the projection, we consider different degrees of loss of effectiveness of the vaccine: 0%, 2.5% and 5% in 10 years.

Figure 27 depicts the total number of infected individuals over time, with different degrees of effectiveness loss.

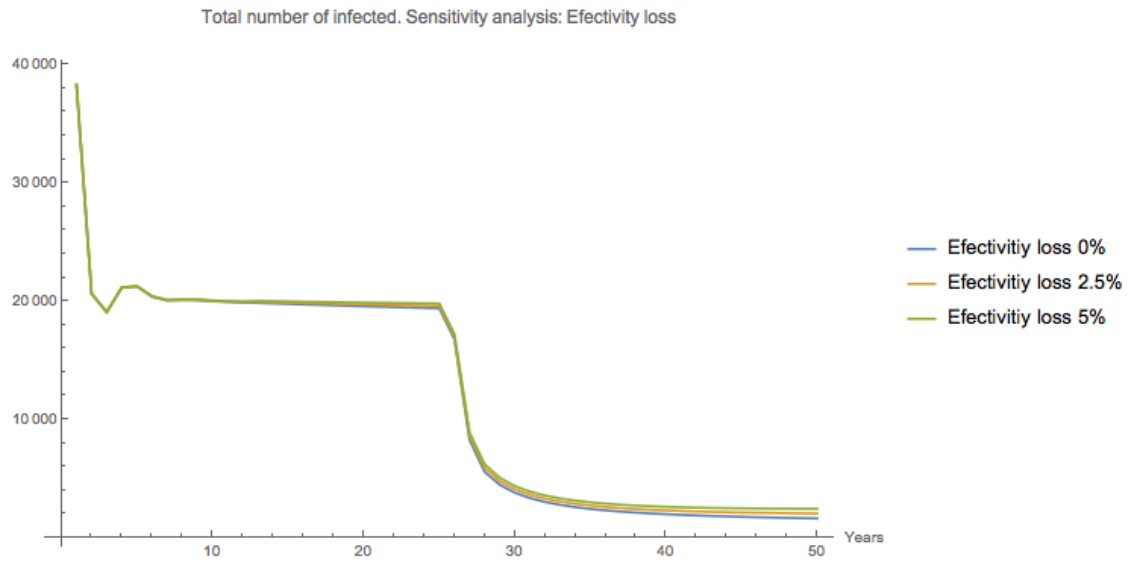

Figure 27. Total number of infected individuals with different degrees of effectiveness loss: 0, 2.5 and 5% in the following 10 years after vaccination, over a period of 50 years.

As it happened before, the scale does not allow us to see the differences, so Figure 28 is a zoom of the lower right part of Figure 27.

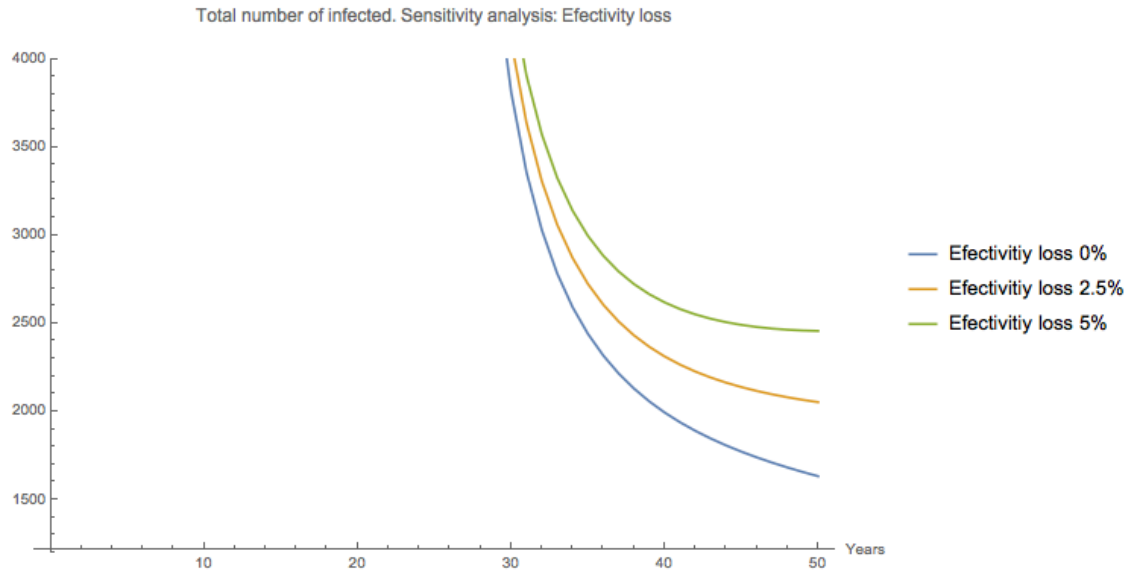

Figure 28. Total number of infected over time, zoom of the main differences between the different degrees of effectiveness loss of the vaccine.

The difference seems not to be relevant until 20 years after the universal vaccination starts, but the difference is more than 1000 varicella cases per year, mainly in adults after 50 years.

5.3. PHARMACOECONOMIC RESULTS

5.3.1. Results.

From a societal perspective, over a 50-year period, varicella total cost averages 12,822,330€ per year in the Valencian Community. Of those, 4.4 million correspond to direct costs, and 8.4 million to indirect costs. (Table 11).

The previous program, where the health system only paid for the catchup vaccine at 12 years of age and risk group children, with no vaccines available for toddlers, the varicella cost decreased by 1.3 million euros per year, which represent 10.4% cost reduction (Table 11), mainly due to a decrease in indirect costs, especially those work days not lost for varicella. Even from the payer's perspective it is a saving program, because the cost of the vaccine is lower that the cost of hospitalizations and primary care attendance, especially when a large number of antivirals are prescribed in adults. These savings also occur in the sensitivity analysis with a vaccination coverage from 80% to 100% with proportional savings, as there is no herd immunity.

Table 11. Average annual cost, over the next 50 years, for vaccination at 12 years and risk groups. In red, the difference (savings) between the costs of each strategy compared to the base case. In blue, the percentage of saving respect to the base case.

		Indirect cost			Difference with base case	
	Payers perspective	Total Indirect cost	Vaccination cost afforded by parents	Total cost	Payers perspective	Total cost
Base case	4,389,925 €	8,432,405 €	0 €	12,822,330 €	-	-
Vaccination at 12 years and risk groups. Coverage 90%	4,384,973 €	7,107,711 €	0 €	11,492,684 €	-4,952 € 0.11%	-1,329,646 € 10.37%

Vaccination at 12 years and risk groups. Cov 80-100%	4,384,573 € 4,385,634 €	6,960,213 € 7,255,187 €	0 €	11,345,847 € 11,639,760 €	-5,352 € -4,291 €	-1,476,483 € -1,182,570 €

With the universal vaccination program, completely paid by the Conselleria de Sanitat, there would be direct savings, of about five hundred thousand euros per year, but taking into account the indirect cost of the vaccine, the savings would nearly reach 8 million euros per year (Table 12).

The change in the vaccination program, if there were no private vaccination, would save 6,5 million euros per year, of those around 4 hundred thousand would be direct costs averted.

Table 12. Average annual cost, over the next 50 years, for universal vaccination. In red, the difference (savings) between the costs of each strategy compared to the base case. In blue, the percentage of saving respect to the base case.

		Indirect cost			Difference with the base case	
	Payers perspective	Total Indirect cost	Vaccination cost afforded by parents	Total cost	Payers perspective	Total cost
Base case	4,389,925 €	8,432,405 €	0 €	12,822,330 €	-	-
Universal vaccination	3,864,028 €	1,050,245 €	0 €	4,914,273 €	-525,897 € 11.98%	-7,908,057 € 61.67%

Any private vaccine program in the toddler saves resources from the payer perspective, as parents pay for the vaccine and the savings of the disease cases adverted are for the payers (Conselleria de Sanitat). But even from the societal perspective, and taking into

account the cost of the vaccine paid by parents, the programs are also cost-saving (Table 13).

As the vaccination coverage increases, the savings from the payers perspective are higher, as the parents pay more for the vaccine at 1&3 years, the health system has to pay for less vaccines at 12 years, and the number of infected children and adults also decreases, as we have seen before, so their cost also decreases. But even for low vaccine coverages, there is a decrease in their cost. The indirect cost increases as the vaccine coverage increases, but most of this cost is due to parents paying for the vaccine, rather than other indirect non sanitary costs as for example work loss. We can see that the vaccination cost afforded by parents increases more than the indirect cost, which means the rest of the indirect costs decrease. The total cost, on the other hand, always decreases as the vaccination coverage increases.

Table 13: Average annual cost, over the next 50 years, for different private varicella vaccination coverages in toddlers. In red, the difference (savings) between the costs of each strategy compared to the base case. In blue, the percentage of saving respect to the base case.

		Indirect cost			*Difference with the base case*	
	Payers perspective	*Total Indirect cost*	*Vaccination cost afforded by parents*	*Total cost*	*Payers perspective*	*Total cost*
Base case	4,389,925 €	8,432,405 €	0 €	12,822,330 €	-	-
Free vaccination						
Cov. 1 & 3: 10%	3,951,754 €	7,190,427 €	738,047 €	11,142,181 €	-438,171 € 9.98%	-1,680,149€ 13.10%
Cov. 1 & 3: 20%	3,514,532 €	7,260,616 €	1,479,873 €	10,775,148 €	-875,393 €	-2,047,182 €

					19.94%	15.97%
Cov. 1 & 3: 30%	3,073,354 €	7,317,211 €	2,225,555 €	10,390,565 €	-1,316,571 € 29.99%	-2,431,765 € 18.97%
Cov. 1 & 3: 40%	2,628,603 €	7,359,710 €	2,975,163 €	9,988,313 €	-1,761,322 € 40.12%	-2,834,017 € 22.10%
Cov. 1 & 3: 50%	2,181,501 €	7,389,310 €	3,728,731 €	9,570,811 €	-2,208,424 € 50.31%	-3,251,519 € 25.36%
Cov. 1 & 3: 60%	1,735,576 €	7,412,297 €	4,486,183 €	9,147,873 €	-2,654,349 € 60.46%	-3,674,457 € 28.66%
Cov. 1 & 3: 70%	1,301,485 €	7,451,302 €	5,247,072 €	8,752,787 €	-3,088,440 € 70.35%	-4,069,543 € 31.74%
Cov. 1 & 3: 80%	912,521 €	7,581,076 €	6,009,692 €	8,493,597 €	-3,477,404 € 79.21%	-4,328,733 € 33.76%
Cov. 1 & 3: 90%	630,673 €	7,943,370 €	6,770,119 €	8,574,043 €	-3,759,252 € 85.63%	-4,248,287 € 33.13%

5.3.2. Sensitivity analysis.

A sensitivity analysis of the cost avoided of the private vaccination with coverage 50% in toddlers and coverage 80 – 100% for 12 years old children, can be seen in Figure 29. The higher the vaccine coverage in toddlers, the less savings, as the number of cases adverted is lower with a large increase in subjects vaccinated.

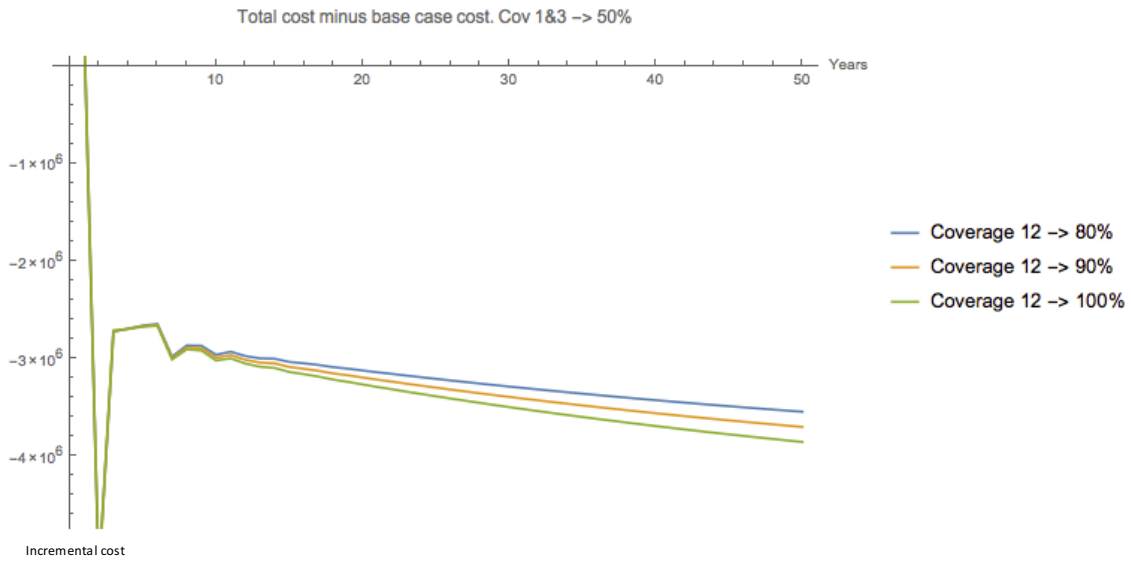

Figure 29: Incremental cost of 50% vaccine coverage with different catch up options at 12 years of age.

The oscillations at the beginning of the Figure 29 appear, as it was mentioned before, because the simulation starts vaccinating only 1-year-old children (with an exceptional saving) and, after two years, the simulation vaccinates 3-year-old children. The oscillation stabilizes after 11 years where a large fraction (80−100%) of the 12 years old susceptible individuals are vaccinated. Nevertheless, the total cost variation is small over the next 50 years.

In 2016, the vaccine public price decreased after reintroduction of the GSK vaccine from 67.91€ to a present cost of 45.38€. Therefore, the sensitivity analysis should include a large variation in the price. Figure 30 shows the total cost of varicella program varying the cost of the vaccine from 30 to 67.91€ per dose. The simulation resembled the previous vaccine situation with a 50% coverage and a 90% coverage for 12-years-old children.

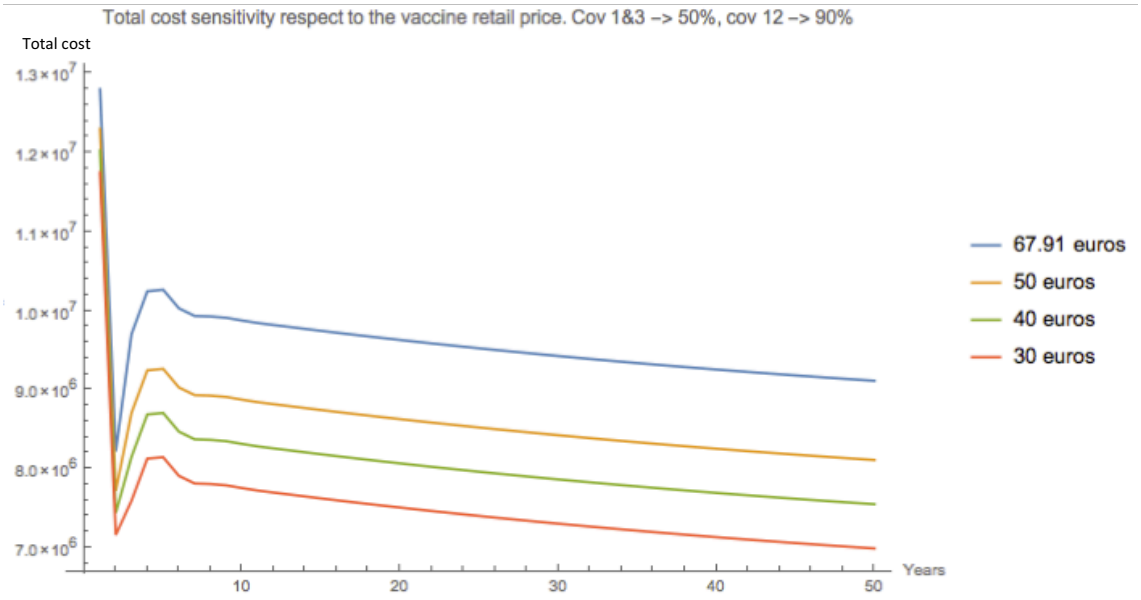

Figure 30: Sensitivity analysis: total cost of the program with different vaccine prices.

5.3.2.1. Cost of the 95% coverage universal vaccination starting 25 years after a 50% coverage.

The estimated cost for a tender is that of the PVL, which for the two vaccines is 29.07 € in 2016. Two scenarios are considered:

1. Universal vaccination with 95% coverage in toddlers at 1 and 3 years of age,
2. Universal vaccination with 95% coverage in toddlers, and catch-up vaccination of the susceptible children of 12 years old with 90% of coverage.

The annual cost of the varicella program, over the next 50 years, for both scenarios, is in Table 14. The cost of maintaining the 12-year-old catch up is higher as the number of cases averted is low, however as they are more severe, this program should be recommended.

Table 14. Annual cost of varicella program

	Payers perspective	Indirect cost	Total cost
Scenario 1	3 719 659 €	1 126 317 €	4 845 976 €
Scenario 2	3 846 815 €	1 066 667 €	4 913 482 €

DISCUSSION

6. DISCUSSION

This study is intended to give answers to a public health concern. Due to the different recommendations of the Spanish Pediatric Association and that of the Public Health, Spanish children achieved a partial protection against varicella with vaccination coverages ranging from 50 to 60% (73) depending of different geographical areas. With that vaccine coverages, there was a potential to shift the infection to older ages as result of the low virus circulation.

To assess the future epidemiology of varicella in Spain, with varying vaccine coverages, we developed a mathematical model, together with the mathematicians at the IM2, Polytechnic University of Valencia. Prof. Villanueva-Micó, Prof. Acedo and Prof. Moraño designed and constructed the model with different mathematical equations under our requirements and using the data provided by us. The calibration of the model and results were interpreted by both teams.

This model has methodological differences with other models previously used to assess the pharmacoeconomic analysis of the vaccine in Spain, and elsewhere, that will be discussed later. The model was fed with actual epidemiological data, and in case of scant or variable data we chose the most conservative to go against the vaccine.

Our model should at least resemble the data reported from the USA, when a universal vaccination program started in 1995 and had increasing vaccine coverage. These data can be summarized as:

1. Decrease in the number of varicella cases: Before the implementation of the vaccine in 1995 in the US, there were 4 million cases of varicella every year in this country. A study by Seward et al., demonstrated personal and herd immunity as a result of vaccinating healthy children in USA. Varicella disease decreased in all age groups, even with moderate vaccination coverages, including infants and adults in all the populations studied (124). A later study, after the second dose was recommended, calculated that the incidence of varicella was nine to ten times lower than in the prevaccine era. It confirmed that varicella vaccine was

effective, with no waning over time. One dose provided protection against moderate to severe disease, and no child of the study developed varicella after a second dose (60). Finally, a meta-analysis was published in 2016, concluding that one dose of varicella vaccine was moderately effective in preventing all varicella and highly effective in preventing moderate/severe varicella, adding the second dose improved protection against all varicella (125).

2. Decrease in the number of hospitalizations: Before the vaccine was administered, 11,000 cases of varicella were hospitalized every year and about 100 patients died. As the number of moderate and severe varicella cases decreased with the introduction of the first dose of vaccine, so did the number of hospitalizations.
3. Decrease in the number of deaths: After 12 years of US varicella vaccination, a study assessed the impact of the vaccination program on varicella deaths. With the first dose of varicella vaccine, the annual average mortality rate for varicella declined 88% in all age groups, with an extremely high reduction among children and adolescents younger than 20 years (97%) and younger than 50 years overall (96%). With the 2 dose program, they believed the severe outcomes of varicella would be eliminated (126).

Varicella vaccine was authorized in Spain in 2004, and Public health recommended the vaccine and paid for it for children aged 12 years with no history of either varicella disease or varicella vaccination (73). This was shown to be the most efficient program as with a very low cost of the vaccine program (very few cases to be vaccinated), prevented the most severe, and expensive cases.

Although toddler vaccination was not included in the official national vaccination schedule, it was recommended by pediatricians and parents paid for it. A vaccination coverage around 50% was reached. In 2013, the Spanish Agency of Medicines blocked the varicella vaccine distribution, and was only available for vaccinating adolescents. This decision was based on a partial coverage of the vaccine that hypothetically could produce a shift of the disease to older ages, where the disease is more severe, and to an increase of HZ cases in adults.

6.1. DISCUSSION OF THE ORIGIN OF THE DATA THAT FED THE MODEL

The population studied was that of the Valencian community. We used the total population, annual birth cohort and age distribution. This was based on the demographic data of the year 2012, the latest data available when the study started.

The incidence of varicella disease was extracted from the British population, as it described the weekly incidence of cases. Spanish data did describe the annual/monthly incidence, but not weekly, necessary for our model. Both distributions were very similar, therefore using the British data is adequate for our epidemiology. It is not expected that using UK data may bias the study (127).

The level of vaccination coverage for routine vaccination program was considered to be similar to the MMRV in Spain, 97.15% (73). The catch-up program is assumed to have the same coverage.

There is a possibility of underreporting in the assessment of the vaccine coverages. A study carried out in Valencia analyzed the vaccination records of Meningococcal C conjugated vaccine (MCCV) and the seroprotection of these same subjects, and showed an underreported rate of vaccinations (128).

The vaccine effectiveness was obtained from a study in Navarra, Spain, and we considered this in our model: 97% after a two-dose schedule (59). The effectiveness of 97% is acquired after the first dose and lasts at least the first 5 years after vaccination. The second dose is administered to maintain this effectiveness for a longer period.

In our model, we assumed 6 months of maternal antibodies protection after birth (112). After this period, the infant can be infected by varicella virus.

After a child is infected, there is a possibility of reinfection. This reinfection is very rare but it is present, and in our model it is based on a variable value. Korostil et al. showed the importance of considering this effect in mathematical models, as the models benefit

showing a periodic behavior as opposed to models that ignore the possibility of repeated varicella attack (129).

Vaccinees can acquire incomplete protection of varicella virus after vaccination and develop a breakthrough varicella. PCR can differentiate between wild type varicella virus or Oka varicella. Wild-type virus can be transmitted from vaccinated individuals with breakthrough varicella to varicella-susceptible individuals. We took this possibility into account, and the transmission rate from breakthrough. The transmission rate from vaccinated individuals to unvaccinated individuals is considered to be 37.1%, which is half the transmission from unvaccinated varicella to unvaccinated, which is about 71.5%, but in our model we considered all the transmission rates the same as for a wild varicella, which is variable per week of the year, as we believe it actually is (63).

The economical data of our model has been extracted from previous studies that did an economic analysis of the varicella vaccine situation, such as Lennes et al (91). Updates are made from the National Statistic Document of 2012, where prices and costs are published every year (73).

6.2. DISCUSSION OF THE DIFFERENT SCENARIOS CONSIDERED.

Different vaccination strategies were considered in the study, and compared with the base-case, when no vaccine is given.

The first approach was the official program in most of the Autonomous Communities of Spain at the time of the start of this project. Only high risk subjects of having a severe varicella, or those reaching 12 years of age and not considered immune to varicella (no history of neither varicella or varicella vaccination) were vaccinated with a two-dose schedule two months apart. This strategy was considered the most appropriate for Spain, as it avoided the most severe cases, occurring in adults, and did not modify the epidemiology of varicella, so that no shift to older ages was expected, neither an impact on zoster, and it was considered the most cost effective program.

However Spanish pediatricians did not consider that this program could avoid most of the disease burden, that occurs early in life, and therefore they recommended individual protection, not considering the potential public health impact of this recommendation (130).

Therefore, different vaccine coverages in toddlers were analyzed so that the different Autonomous Communities of Spain may estimate the future epidemiology of varicella.

Finally, a universal vaccination program, resembling the one in the US and other areas of the world, and that was 'required' by pediatricians, was also considered.

During the development of this work, public health unexpectedly decided to incorporate the varicella vaccine into the National Immunization Program, as a response to social pressure, so we modified the model to assess the impact of this program on the epidemiology, this program, then, consisted of moving from partial to universal vaccination. To our knowledge this is the first time this change in a program is analyzed.

Our main concern at the beginning of the study was to assess the impact of different vaccination strategies on the varicella in adults. We expected to assess the potential shift of cases to adults and to estimate the impact of the private vaccination in toddlers

in the preadolescent program. We hypothesized that a partial vaccination coverage in toddlers would drive to more children reaching the age of 12 not immune to varicella due to the herd effect of the vaccine. That would also mean an increased cost of the official recommendation.

6.3. DISCUSSION OF THE MATHEMATICAL MODEL

Although varicella epidemiology and the impact of the vaccine has been modelled previously (even the impact in Spain), we developed a more sensitive model where the herd effect is important, and studied the impact of a catch up program at 12 years of age on the epidemiology. Besides we included an economic model that would help the decision makers towards different vaccination strategies.

We initially simulated the disease with a network model. We chose this model as they give very accurate results in epidemiological analysis. In these models, the spread of infectious diseases is determined by random encounters among people who live in the same geographical area: meeting at the bus stops, crossing in the streets, gathering at shop centers, playing in the playground or attending day care centers. A joined study of the IM2 mathematicians and FISABIO could reproduce the epidemiology of different infectious diseases, as RSV (122). However, when trying to develop this model, it showed complicated evolution patterns reminiscent of chaotic behavior (the disease disappeared in the population), so we abandoned this method and opted for a more classical model of difference equations with variable coefficients. This is much in the tradition of mathematical epidemiology, and we have used this in the epidemiology of varicella.

The first model developed by Halloran et al. (99) was used later by Lenne et al (91), to assess the pharmacoeconomy of universal varicella vaccination in Spain. This model had some limitations for our interest, as they only used one vaccine dose, and the age groups considered were not ideal for the assessment of the various programs at age 12 years and later. The model here described has five stages, from the patient being susceptible, to infected and finally recovered, one more than Halloran's, as we considered important, from the epidemiological point of view a two-stage latency period, one not being infectious and the following one being infectious without skin lesions or other symptoms.

And what is more important, our model considered five age groups that allowed a finer tune of the epidemiology, and especially in subjects older than 12 years of age.

Using the transmission function described by Halloran, and used also by Lenne, the model had unrelievable epidemiological patterns. We forced the model so that it gave that the transmission of the virus was different depending on the week of the year, so we determined weekly transmission values. This variation in the transmission, that may be related to climatic variations, could partly explain the different epidemiology of varicella in temperate and tropical climates.

It is a very conservative model, in case of lack or scarce information in a topic, we opted for the inclusion in the model of the most conservative data, always trying to go against the vaccine. For example, we assumed a loss of effectiveness of 1% per year starting 15 years after the administration of the second dose of the vaccine. There is no data in the literature to support this assumption, but there is always a potential loss of immunity. We also considered the stage Latency 2, which is the stage where the patient is contagious but still does not have skin vesicles to be 1 week long, when the real period is estimated to be 24-48 hours long, only reaching 1 week in case of immunocompromised patients. This way, we increased the transmission of varicella, increasing the number of patients that would be infected as there would be no isolation of the patients. Breakthrough cases are considered to be as infective as primary wild type virus varicella cases, which is more infective than what other models have considered, and we also included in our model the cost of these cases and assumed they had the same cost as the rest of varicella cases.

With this model we wanted to describe how the disease would behave with different vaccination strategies, in order to assess the decision-making teams and help them take the correct decision regarding the varicella vaccination strategy that is better for our community. To complete the research, economic data were introduced in the dynamic model to assess the pharmacoeconomic impact of the vaccine, so this can not be a reason to decline the introduction of the vaccine.

HZ is another of the reasons why the Spanish Medicine Agency withdrew the vaccine, they thought it would increase substantially after universal vaccination. We did not include HZ in our model because it has been demonstrated that the increase of HZ in US

has not changed the slope after the introduction of the vaccination and it is probably due to other reasons, as explained previously.

The children are considered to be immune after the first vaccine administered, this means, at 1 year of age if they receive the vaccine, because the second dose was initially added to the vaccination calendar because a loss of efficiency and therefore immunity was observed after few years of the first administration of the vaccine. This means, after the first vaccination the children is totally protected, at least for the first two years until he receives the second dose, which will boost immunity and the subject will be protected for many more years. We wanted to go "against" the vaccine so the model would be less criticized, for this reason, we assumed a loss of effectiveness of the vaccine of 1% per year starting 15 years after the administration of the second vaccine.

Our model has some weaknesses that we must assume. First of all, we consider that every child that receives the first dose of vaccine as a toddler will receive the second dose too. This is what our experience has proven in the Valencian Community, as more than 90% of the children who receive a first dose of a vaccine, even if paid by parents such as Rotavirus vaccine, receive the second dose. The official data of the Valencian community of 2015 are 91% first dose and 86% second dose, based on the Vaccine Information System of Valencia, but the data is not updated daily and this can alter the population and vaccination data (128).

Transmission data that is not taken into account is that children who are vaccinated or reinfected are less infectious than other children. Also, as the virus stops being transmitted, there is no immunity boost in the population, and more people could get reinfected, but this is balanced by the fact that there is less virus circulating, and therefore less people will be in contact with the virus and there is less probability for them to get infected. This means, less immunity boost which could increase the incidence of varicella but less virus circulating, which cancels this increase.

In order to calibrate the model, we used British data, that gave the incidence of cases per week for 4 seasons. We consider that the distribution of the population and the infection is like the one found in the Valencian community.

Another possible weakness of our model is that the stages of the disease are not all one week long, for example, from the moment the patient is infectious (L2) but still does not have vesicles until it finally has skin lesions, the average time is 24-48 hours, not one week, except in immunocompromised patients. Some people even believe this period does not exist in healthy patients, as some lesions can be found in the scalp but are not looked for. Again, we decided to be conservative and increase the contagiousness of varicella, increasing the number of patients that would be infected as there would be no isolation of the patients. With this assumption the calibration of the model is very precise, which reassures our model.

The major criticism of this model is that we did not take into consideration HZ. It has been recommended that a pharmacoeconomic analysis of varicella vaccine should not only take into consideration varicella disease but also HZ, as these are the complete picture of VZV disease. However, the relationship between varicella virus circulation and the reactivation of the latent virus in the dorsal ganglia remains still unclear.

In 1965, Hope-Simpson hypothesized about the transmission of herpes zoster and other important aspects of the disease (1). He believed some factors could interfere in the decline of antibody and prolong the latent interval. He thought that each reactivation of the virus in the ganglia is likely to stimulate the immunity. Antibody values and cell-mediated immunity (CMI) are initially high but they decline, and it is possible that a exogenous stimulation may boost immunity. He linked viral replication and clinical disease to CMI, which controls replication and reactivation of the virus, maintaining it subclinical and asymptomatic by contained reversions. He described the possibility that the boosts are due to extraneous simulation. Each time a person who has had varicella encounters an infectious case of varicella or zoster, he may get in contact with the virus and this might boost his immunity.

Brisson et al. developed a model to simulate varicella dynamics after vaccination and also HZ after varicella vaccination. This model was based in the Hope-Sympson Theory, that was cuantified by Thomas (131) in a case control study. Brisson showed a potential danger of an increase in zoster cases following reduction in varicella cases due to vaccination, that could be explained partially by Hope-Simpson's theory. They explained

how very effective programs in terms of varicella reduction could be harmful to public health in terms of zoster morbidity (64).

Ogunjumi et al. developed an individual-based model to assess the effect of varicella vaccination on shingles (132). It suggests that re-exposure to the virus will provide an exogenous boost, but the protection will only last about one or two years, which is a much shorter time than previous predictions suggested. It also predicts that the number of shingles will increase 31 years later, but this increase would be temporary. This increase is predicted to occur among 31 to 40-year-olds, not in older age groups as expected, and therefore would probably have less complications of shingles.

There is an open debate about how varicella vaccination may modify the incidence of herpes zoster. However, this has not happened in the United States fifteen years after the introduction of the varicella vaccine. There has been an increase of HZ in the US that started long before the vaccine was developed, but the slope of this increase has not been modified with the introduction of the vaccine. There are several causes that may have increased the number of patients that suffer herpes zoster, such as the aging of the population and the increase of immunosuppressed patients such as cancer patients, transplant survivors and stressed people (2).

Brissons et al. assumption seems incorrect, and a study developed in France and observing incidence of zoster in cloistered nuns and monks without contact with children and general population demonstrated there has not been a change in the slope of the increase of zoster, as both populations had the same incidence of the disease (66).

In summary, different studies show no consistent increase of herpes zoster incidence in the United States since the varicella vaccine program started, so the doubt is still present.

The main weaknesses of our model can be summarized in:

- All the vaccinated children receive two doses, this means, every child that receives the first dose of vaccine as a toddler will receive the second dose too.
- Breakthrough varicella cases and reinfections are less infectious than primary wild type varicella cases, but we considered them to be the same.
- Weekly distribution of the varicella is based on English population.
- The stages of latency and infectious are not weekly, but we measure them this way.
- While infections decrease number, there is less community booster, but also less virus circulating, therefore we consider the infectious rate the same.
- Herpes zoster is not taken into account in our model, based on the published literature as we reviewed previously.

Even though it has some possible weaknesses, the model simulates the disease in our population almost exactly, in incidence, per group ages and weekly distribution.

6.4. DISCUSSION OF THE RESULTS OF OUR STUDY

Regarding the epidemiological results the model gave us, the results were very similar to the expected ones, especially if compared to what has happened in USA during the last 20 years (133). In our model, the base case is considered the epidemiology of the varicella disease without any vaccination. We compared to these different distributions of the disease depending on the vaccination strategy. All the other strategies consider a vaccination program at 12 years of age in children without history of varicella or vaccination of this disease.

In every case, compared to the base case, the number of varicella cases in all ages decreased. It especially decreased in people older than 12 years of age. In the total number of infected for all ages, with a vaccine coverage in toddlers of 0%, the number of total infected still is under the base case, because the catch up is still being administered. While the coverage increases, the number of total infected decreases, until reaching almost 0 when the coverage in toddlers is about 90%.

In children younger than 12 years of age, the number of infected children also decreases as the coverage increases. The decrease for a 0% coverage is very mild compared to the base case, as no children are vaccinated, but this small decrease is due to the herd immunity that is produced by the 12-year-old catch up.

On the other hand, for subjects older than 12 years, the decrease is more pronounced. At this age, the disease is much more severe, and any shift of the disease to these ages must be anticipated by the model. This is the main reason why the vaccine was stopped being administered to toddlers, so we should carefully describe what would happen with different vaccination coverages. In this age group, there is a decrease in the total number of infected with every vaccination coverage, even without a toddler vaccination program due to vaccination at 12 years of age. This means, that with a catch up program at 12 years of age, the number of infected individuals older than this age is always lower than in the base case, even with low-medium vaccine coverages in the toddler. With this results of our model, we are proving what has been seen in USA, there is no shift of the disease to older ages with any vaccination coverage. In fact, as the coverage increases,

the number of cases decrease for at least over the next 50 years, and the trend is to keep decreasing.

These trends do not change too much when the sensitivity analysis is done and we assume a loss of immunity of 1% per year starting 15 years after the complete schedule at 3 years. For the total number of infected at any age, there is a slight increase of cases compared to previous results, but even with this, there is a very important difference between the number of infected in the base case and 0% coverage with the rest of coverages, which means there is always a decrease in the number of infected when vaccination to toddlers is started.

Taking into account this loss of immunity, in subjects over 12 years of age the effect of immunization loss is visible. There is an increase in the total number of infected individuals as time goes on and coverage increases. This means, that this loss of immunity is more important in patients older than 12 than in the total population, as it is at these ages when the loss of immunity is higher as more years have gone by. But even so, the number of cases in older subjects is always lower than in the base case, which means the disease will not shift to older ages in any case, not even if this loss of immunity occurs.

The next question is: what is the number of susceptible subjects reaching 12 years of age? Or what is the same, how many children should be vaccinated when they reach 12 years of age? The number of susceptible individuals that reach the age of 12 is higher for low vaccine coverages than the base case, as there is less virus circulating and less children become infected. For low vaccine coverages, up to 70%, the number of susceptible individuals at 12 increases, and is much higher than the base case. Once coverage reaches 80%, this number decreases suddenly, but it is still over the base case. It is only after vaccinating as toddlers 90% of the population or more when the number of susceptible individuals decreases under the base case, this is because in the base case, the number of infected individuals before 12 years is more than 90% of the population, and therefore 90% of the population will have to be vaccinated to equal this number, but the decrease will be even bigger due to herd immunity, where children that are not

vaccinated will not suffer from varicella because there will be less virus circulating in the population.

The number of susceptible individuals at 3 years of age that are also susceptible at 12 years is similar for different vaccine coverages until 60-70%, and represent the number of varicella cases during childhood. The percentage of susceptible at both ages is low with low coverages, because as there is no initial herd immunity, most of the children will suffer from varicella and therefore will not be susceptible at the age of 12. But with higher coverages, over 70%, there is a change in the evolution and herd immunity effect produces a remarkable increase in the percentage of susceptible individuals, as they are not infected while they are younger. However, these non-vaccinated susceptible are better protected against infection because of the herd immunity.

The economic analysis should also be discussed. Varicella disease is an expensive vaccine, the average cost per year without vaccine is almost 13 million €. With the introduction of the catchup vaccine at 12 years, the cost decreased by a 10.4% (almost 1.5 million €), mainly due to indirect costs, especially work days not lost for varicella. The cost of the vaccine is lower than the cost of hospitalizations and primary care attendance, especially when a large number of antivirals are prescribed, so it is even cost saving for the payer's or health system's perspective.

In case the vaccine was paid by the Regional Government even for children at 1 and 3 years, there would be direct savings, of about five hundred thousand euros per year, but taking into account the indirect cost of the vaccine, the savings would nearly reach 8 million euros per year, which means almost 62% savings of the total cost.

Compared to the present program, i.e. vaccination at 12 years of age, a universal vaccination program would save 6,5 million euros per year, of those around 400,000 would be direct costs averted. Thus, even if the government paid for the toddlers and catch up vaccine, there will be savings of the total cost and from the payers perspective.

The last economic option analyzed is toddlers vaccination at 1 and 3 years paid by parents and catch up paid by the system. We called this free vaccination, as parents

decide if they vaccinate their children, pay for it, and vaccines are available for them. We studied different vaccination coverages for this economic situation. As the vaccination coverage increases, the savings from the payers perspective are higher, as the parents pay more for the vaccine at 1&3 years, the health system has to pay for less vaccines at 12 years, and the number of infected children and adults also decreases, so their cost also decreases. For example, for a high coverage such as 80%, the savings from the payers perspective are about 79%, and total saving 34%.

But even for low vaccine coverages, there is a decrease in their cost, a 20% coverage will save 20% from the payers perspective and 16% of the total cost. The indirect cost increases as the vaccine coverage increases, but most of this cost is due to parents paying for the vaccine, rather than other indirect non sanitary costs as for example work loss. We can see that the vaccination cost afforded by parents increases more than the indirect cost, which means the rest of the indirect costs decrease. The total cost, on the other hand, always decreases as the vaccination coverage increases.

In summary, as the coverage increases, the cost from the payers perspective and the total cost decrease, which means there will never be a loss of money when vaccination for toddlers is available for the population, no matter what the coverage is.

The results of the study have been very useful; we were able to demonstrate with an accurate model that there were no solid reasons for the withdrawal of the varicella vaccine. The disease is not expected to shift to older ages, no matter what the coverage at 1 and 3 years of age is, and economically, it is always going to be cost saving.

The main goal of this study is to assess the epidemiology of varicella after different vaccination strategies and vaccination coverages in order to advise decision-making people about whether or not the varicella vaccine should be administered, when and where this could be done, and who should pay for these doses. This goal has been achieved, and recommendations can be done about different strategies.

This model is a valid tool to propose different situations with the disease, we can model the future epidemiology in a long term with any immunization schedule. Besides, it can

be modified in order to simulate other diseases by changing parameters such as: infectivity, weekly variation, age distribution, etc.

CONCLUSIONS

7. CONCLUSIONS

7.1. GENERAL OBJECTIVE

1. Estimate the impact of different vaccination strategies in the Valencian Community:
    a. The total number of cases of varicella will decrease when a catch up vaccine is administered at 12 years of age, regardless of the vaccine coverage at 1 and 3 years of age.
    b. The total number of infected older than 12 years of age will not modify with the administration of the varicella vaccine to toddlers, regardless of the vaccine coverage at 1 and 3 years of age. Thus, there is a decrease in the total number of cases and no shift to older ages.
    c. Even if there is a loss of immunity of 1% per year starting 15 years after the administration of the vaccine, the total number of cases after vaccination will still be lower than the number of cases without it.
    d. Important herd immunity is shown when the vaccination coverage at 1 and 3 years of age is higher than 70%. Below this, the main effect of the vaccine is the direct protection to the vaccinated.
    e. The number of susceptible 12 year olds is higher than the base case, but when it reaches a 70% coverage it starts decreasing due to herd immunity and when it is over 80%, the number of children that reach the age of 12 being susceptible is much lower than the base case.
    f. This leads to an increase of vaccinations to 12 year olds when there is a low toddler vaccination coverage.
    g. It is essential that the catch up program is maintained until all the infant population has vaccination coverages over 90%.

7.2. SPECIFIC OBJECTIVES

Varicella vaccine is highly efficient in the prevention of varicella. In all the programs described the vaccine saves resources, from the payer and from the societal point of view.

2. Evaluate the impact of partial varicella coverage on the incidence of varicella in adults.
    a. The total number of infected older than 12 years of age will not modify with the administration of the varicella vaccine to toddlers, regardless of the vaccine coverage at 1 and 3 years of age. Thus, there is a decrease in the total number of cases and no shift to older ages.
    b. Even if there is a loss of immunity of 1% per year starting 15 years after the administration of the vaccine, the total number of cases after vaccination will still be lower than the number of cases without it.

3. Calculate cost-benefit effect of universal vaccination strategy in Valencian Community.
    a. Universal vaccination with a two-dose schedule would save resources not only to the Health System but also to the whole society. These savings are higher than previously described and are due to an increase in the costs of the health system and an increase of the salaries in Spain in the last 10 years, while the cost of the vaccine remains the same or is slightly lower.
    b. The costs saved by the health system are more than half a million euros. The total cost savings are almost 8 million euros.

4. Calculate cost-benefit effect of risk group and preadolescent strategy in Valencian Community.
    a. With the present situation strategy, for a coverage of 90%, the savings for the Health System are less than 5,000 euros, and 1.3 million euros of the total cost, which includes indirect costs.

5. Calculate cost-benefit effect of individual non systematic and preadolescent strategy in Valencian Community.
    a. A free vaccination program would save between 0.5 and 3.1 million euros per year to the Health System, and between 0.98 and 1.24 millions of indirect costs, depending on the vaccine coverage.

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PUBLICATIONS AND CONGRESS PRESENTATIONS

9. PUBLICATIONS AND CONGRESS PRESENTATIONS

PUBLICATIONS

Díez-Gandía A, Villanueva R-J, Moraño J-A, Acedo L, Mollar J, Díez-Domingo J. Studying the Herd Immunity Effect of the Varicella Vaccine in the Community of Valencia, Spain. In: Ortuño F, Rojas I, editors. Bioinformatics and Biomedical Engineering: 4th International Conference, IWBBIO 2016, Granada, Spain, April 20-22, 2016, Proceedings. Cham: Springer International Publishing; 2016. p. 38-46.

CONGRESS PRESENTATIONS

2015 Poster Presentation. "Epidemiologic and economic impact of non-funded varicella vaccination with medium-high vaccine coverage in Spain." Díez-Gandía A, Villanueva R.J, Moraño J.A, Acedo L, Mollar J, Díez-Domingo J. 33rd Annual Meeting of the European Socitey for Pediatric Infectious Diseases, ESPID. Leipzig, Germany.

2015 Poster Presentation. "Herd immunity with partial varicella vaccination coverage. Epidemiological model." Díez-Gandía A, Villanueva R.J, Moraño J.A, Acedo L, Mollar J, Díez-Domingo J. 33rd Annual Meeting of the European Society for Pediatric Infectious Diseases, ESPID. Leipzig, Germany.

2015 Oral Communication. "Análisis económico de la vacuna de la varicela con cobertura media." Díez-Gandía A, Villanueva R.J, Moraño J.A, Acedo L, Mollar J, Díez-Domingo J. Congreso Asociación Española de Vacunología, AEV. Córdoba, Spain.

2015 BEST POSTER PRESENTATION. "Efecto comunitario de la vacuna de la varicela. Modelo epidemiológico." Díez-Gandía A, Villanueva R.J, Moraño J.A, Acedo L, Mollar J, Díez-Domingo J. Congreso Asociación Española de Vacunología, AEV. Córdoba, Spain.