Preventive effectiveness of varicella vaccine in healthy unexposed patients

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Palabras clave vaccine, varicella, Epistemonikos, GRADE.

Abstract

Introduction

Chickenpox is an infectious disease caused by Varicella Zoster virus. Varicella vaccine is conventionally used for its prevention, and its administration seeks to reduce the onset of the disease and complications associated. However, there is still controversy about its effectiveness.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified two systematic reviews including 16 studies overall, of which three were randomized trials. We concluded that the varicella vaccine decreases the risk of contracting the disease in the long term and probably reduces the risk of developing the disease in the short term in healthy unexposed patients. Nevertheless, the vaccination increases the occurrence of local reactions 48 hours after its administration and probably increases the presence of fever and chicken pox-like rash.

Problem

Chickenpox is an infectious disease caused by Varicella Zoster virus. Most cases occur in childhood (under 14 years old), so it has been identified as an important cause of school absenteeism, generating significant expenses to the community[1,2]. Chickenpox diagnosis is clinical, characterized by pruritic, vesicular, cephalocaudal, polymorph rash, with scalp involvement, generally associated to fever.

Usually, varicella vaccine is used for disease prevention, which is a live attenuated vaccine that induces humoral immune response. Its administration would prevent the onset of disease and its complications. However, there is still controversy regarding its effectiveness in reducing chickenpox in the short and long term.

Key messages

- Vaccination against chickenpox decreases the risk of developing the disease in the long term.
- Vaccination against chickenpox probably decreases the risk of developing the disease in the short term.
- Vaccination against chickenpox increases the occurrence of local reactions 48 hours after its administration and probably increases the presence of fever and chickenpox-like rash.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified two systematic reviews[3,4], which including 16 primary studies reported in 17 references[5-21], of which two correspond to randomized trials reported in three references[19-21]. This table and the summary in general are based on the latter, since observational studies did not increase the certainty of existing evidence, nor did they provide additional relevant information.
What types of patients were included*	All trials included healthy patients, with no history of chickenpox or vaccination against the disease. One trial included patients between one and 14 years old[20], while the other trial included patients between 10 to 30 months old[21].
What types of interventions were included*	All trials evaluated one dose of Oka strain varicella vaccine[20,21]. Both trials compared vaccination against an unvaccinated control group[20,21]. In addition, one of the trials included a comparison with no follow-up of the control group[20], so in this summary the authors decided to evaluate it assuming the worst case scenario, meaning that no one in the unvaccinated control group develop chicken pox in the follow-up years.
What types of outcomes were measured	Trials reported multiple outcomes, which were grouped by systematic reviews as follows: • Development of chickenpox disease. • Percentage of vaccinated patients. • Disease rate among unvaccinated participants. • Time between vaccination and disease occurrence. • Adverse effects: fever, local reactions, "chickenpox-like rash". • Transmission of chickenpox from vaccinated individuals to others. • Risk of herpes zoster following vaccination. • Variations in age presentation. • Cost-effectiveness for varicella vaccine. The average follow-up of the trials was 40 months[20,21], with a range between nine months[21] and seven years[20].

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a preestablished format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Summary of findings

Information about varicella vaccine effects is based on two randomized trials that included 1449 patients.

Both trials measured short-term chickenpox and chickenpox-like rash as outcomes[20,21] (1407 patients). One of the trials measured long-term chickenpox, fever and local reactions (914 patients) [20]. No trial reported the outcome severe or complicated chickenpox.

The summary of findings is the following:

- Vaccination against chickenpox probably decreases the risk of developing the disease in the short term (moderate certainty evidence).
- Vaccination against chickenpox decreases the risk of developing the disease in the long term (high certainty evidence).
- Vaccination against chickenpox probably results in little or no difference in the onset of fever after administration (moderate certainty evidence).
- Vaccination against chickenpox increases the occurrence of local reactions within 48 hours after administration (high certainty evidence).
- Vaccination against chickenpox probably increases the appearance of chickenpox-like rash after administration (moderate certainty evidence).

Effectiveness of varicella vaccine in healthy unexposed patients

Patients Healthy patients not previously exposed
Intervention Varicella vaccine
Comparison Not vaccinated

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT vaccination	WITH vaccination		
	Diferencia: pacientes per 1000			
Short term chickenpox	132 per 1000	11 per 1000	RR 0.08 (0.00 a 1.66)	⨁⨁⨁◯[1,2,3] Moderate
	Diferencia: 121 lee (Margen de error: 132 to 87 less)			
Long term chickenpox	87 per 1000	49 per 1000	RR 0.56 (0.34 a 0.93)	⨁⨁⨁⨁ High
	Diferencia: 38 less (Margen de error: 58 to 6 less)			
Fever	20 per 1000	21 per 1000	RR 1.06 (0.43 a 2.58)	⨁⨁⨁◯[1] Moderate
	Diferencia: 1 more (Margen de error: 12 less to 32 more)			
Local reactions in 48 hours	191 per 1000	271 per 1000	RR 1.42 (1.12 a 1.81)	⨁⨁⨁⨁ High
	Diferencia: 80 more (Margen de error: 23 to154 more)			
Chickenpox-like rash	25 per 1000	40 per 1000	RR 1.63 (0.92 a 2.96)	⨁⨁⨁◯[1] Moderate
	Diferencia: 15 more (Margen de error: 2 less to 48 more)			
Severe or complicated chickenpox	No information on this outcome was found in the analyzed evidence		--	--

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT vaccination** is based on the risk in the control group of the trials. The risk **WITH vaccination** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded in one level for imprecision, since each end of the confidence interval involves a different decision.
[2] The certainty of the evidence was downgraded in one level for inconsistency due to different studies reached different conclusions (I2 = 79%).
[3] The certainty of the evidence was upgraded in one level for large magnitude of an effect with a RR <0.2.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented applies to healthy children and adolescents not previously exposed to chickenpox disease.

It does not apply to exposed or immunosuppressed patients, with direct exclusion of these in clinical trials. These patients could present different clinical outcomes than those described, which would be determined by variations in their immune response to the vaccine.

About the outcomes included in this summary

The outcomes selected are those considered critical for decision-making, according to the opinion of the authors of this summary and generally coincide with those evaluated by the systematic reviews identified.

However, the reviews do not report the outcome of severe or complicated disease, which was considered a critical outcome as it implies greater morbidity and mortality, as well as an increase in costs for the community[1,2].

Balance between benefits and risks, and certainty of the evidence

The evidence shows benefits associated with vaccination in preventing chickenpox disease development both in the long and short term. On the other hand, the application of the vaccine is associated with the occurrence of adverse effects, but these are mild and have little clinical relevance.

Considering that the certainty of evidence of the results presented in this summary is moderate or high, the balance between benefits and risks favors the administration of the vaccine.

Resource considerations

Considering that chickenpox is a highly prevalent disease, which causes school absenteeism and significant expenses, it seems appropriate to invest resources in the vaccination of healthy patients prior to exposure, since it decreases disease development.

A systematic review about the economic analysis of vaccines in Spain from 1990 to 2012 concluded that the administration of the varicella vaccine seems to be justified in children aged 15 to 24 months if the indirect cost of suffering the disease is considered[22]. Another Italian systematic review concluded that the implementation of universal vaccination in all regions of Italy by 2015 would be cost-effective from a social perspective, and would imply a favorable cost-effectiveness profile from the NHS perspective[23].

What would patients and their doctors think about this intervention

With the information provided in this summary, most clinicians should recommend vaccination against chickenpox, since there is evidence of a significant decrease in the incidence of the disease, without severe adverse events associated.

However, there could be variability regarding this intervention in clinical decisions made by patients, especially those with personal ideologies regarding vaccination or those who insist on the usually benign and self-limited course of disease.

Differences between this summary and other sources

These conclusions agree, in general, with systematic reviews identified regarding the outcome of incidence of chickenpox disease after the administration of the vaccine and its adverse effects.

The key messages of our summary are consistent with the recommendations of the Advisory Committee on Immunization Practices, which suggests the application of the varicella vaccine in patients who have not had the disease[24].

Could this evidence change in the future?

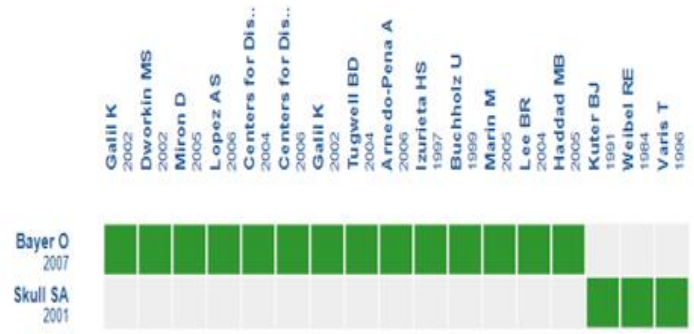
It is unlikely that future evidence will change the conclusions of this summary, because of the high certainty of the evidence related to the development of the disease in the long term. The conclusions regarding adverse effects could change, since they present moderate certainty evidence, excluding the appearance of local reactions whose certainty of the evidence is high.

We did not identify ongoing trials answering this question in the International Clinical Trials Registry Platform of the World Health Organization.

We did not identify systematic reviews in progress in the PROSPERO register (International prospective register of systematic reviews).

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Effectiveness of varicella vaccine in healthy unexposed patients

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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