Vaccination of children with a live-attenuated, intranasal, influenza vaccine
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Background
Influenza is a global infectious disease of the respiratory tract, caused by influenza viruses A or B that annually causes high morbidity and mortality in Germany.

Influenza is preventable by vaccination and the vaccination is recommended by the The German Standing Committee on Vaccination (STIKO) as a standard vaccination for people from the age of 60 onwards. Up to date a parenterally administered trivalent inactivated vaccine (TIV) has been in use almost exclusively. Since 2011 however a live attenuated vaccine (LAIV) has been approved additionally. The STIKO most recently recommends LAIV for children from 2 to 17 years of age, within the scope of indication vaccination.

A person who has had influenza generally has protection against the original influenza pathogen ("immunological memory"), but due to the continuous change in influenza viruses (antigen drift) this does not provide reliable protection against reinfections that recur annually or seasonally – which applies in the same way to immunity provided by vaccination. For this reason, influenza vaccination has to be repeated every year.

Both with regard to their own morbidity and their role in spreading influenza to other age groups, children are regarded as a particularly important target group for influenza vaccination. Since annual / seasonal influenza epidemics do not spread across all age groups simultaneously but initially affect children in the main, general vaccination of children might also impact positively on herd protection.

The objective of this Health Technology Assessment (HTA) is to address all various research issues regarding the vaccination of children with LAIV. The analysis was performed from a medical, epidemiological and health economics perspective, as well as from an ethical, social and legal point of view.

Objectives
Medical research questions
- How efficacious is LAIV in the vaccination of children and teenagers up to the age of 18 against influenza as compared to other interventions or placebo?
- How safe is LAIV as an influenza vaccine for children and teenagers up to the age of 18 as compared to other interventions or placebo?
- Are there any differences regarding the efficacy and safety of LAIV relative to certain factors?
- From a medical perspective, where is there a need for further research as a result of inconsistent study results or a lack of studies?
Epidemiological research questions

- How effective is LAIV in the vaccination of children and teenagers up to the age of 18 against influenza as compared to other interventions, placebo or non-intervention?
- How safe is LAIV as an influenza vaccine for children and teenagers up to the age of 18 as compared to other interventions, placebo or non-intervention?
- Do indirect protective effects occur due to influenza vaccination of children and teenagers up to the age of 18 (herd protection)?
- Are there any differences regarding the efficacy and safety of LAIV relative to certain factors?

Economic research questions

- What is the cost-effectiveness of vaccinating children and teenagers up to the age of 18 against influenza?
- Is the use of LAIV as an influenza vaccine for children and teenagers up to the age of 18 a cost-effective option?
- What is the potential budget impact of LAIV?
- From a health economic perspective, where is there a need for further research as a result of inconsistent study results or a lack of studies?

Ethical / social / legal research questions

- What preferences are enjoyed by children and teenagers up to the age of 18, their parents/custodians and society at large with regard to influenza vaccination? Are there any ethical conflicts between child/parent self-determination regarding vaccination and society's desire for general immunity (herd protection)?
- In the case of children and teenagers up to the age of 18, what factors influence an individual's decision in favor of or against influenza vaccination? What is the impact of the method of administration and physicians' recommendations?
- What is the current situation regarding access to influenza vaccination in general and specifically to the various vaccines in Germany? How do you rate the practice of cost reimbursement?
- What other legal aspects have to be considered?

Methods

An extensive systematic database research was performed to obtain relevant information. In addition a supplementary research by hand was done. Identified literature (full-text) was screened using predefined inclusion and exclusion criteria. Each item was reviewed by two independent appraisers and evaluated with regard to content. Included literature was evaluated in full-text using acknowledged standards.

Results

Medicine

Efficacy

In the case of children aged 6 months to ≤7 years, LAIV is superior both to a placebo and to vaccination with inactivated influenza vaccine (TIV) (approx. 80% and approx. 50% respectively). The evidence level for children in the general population (i.e. concomitant disorders were not an inclusion criterion) and for children with asthma in this age group was assessed as being high. In the case of children aged >7 to 17 years (= 18th year of their lives), LAIV is superior to vaccination with inactivated influenza vaccine (TIV) (approx. 32%). The evidence for this statement originates from a randomized, open study that was conducted on children with asthma over the period of an influenza season. No studies comparing LAIV with placebo that reported on the efficacy of LAIV with respect to laboratory confirmed influenza infection were identified for this age group. It can be concluded that there is high evidence for superior efficacy of...
LAIV (compared to placebo or TIV) among children aged 6 months to ≤7 years. For children from >7 to 17 years, there is moderate evidence for superiority of LAIV for children with asthma, while direct evidence for children from the general population is lacking for this age group. Due to the efficacy of LAIV in children aged 6 months to ≤7 years (high evidence) and the efficacy of LAIV in children with asthma aged >7 to 17 years (moderate evidence), LAIV is also very likely to be efficacious among children in the general population aged >7 to 17 years. Since this evidence is indirect, its level has to be classified as low.

Safety
In the included studies with children aged 2 to 17 years, LAIV was safe and well-tolerated. The most frequent side effects were local reactions to the vaccine (rhinitis) and general signs of reactogenicity. Mortalities potentially associated with the vaccine were not reported in the included studies. Information is available from one study indicating that in children aged 6-11 months LAIV leads to a higher rate of hospitalizations with any cause than TIV and to a higher rate of serious adverse events. From the same study there is information indicating that in children aged 6-24 months LAIV leads to a higher rate of acute wheezing. Based on these results the use of LAIV was restricted to children aged 24 months up to the age of 18 in the EU.

Sociodemographic factors
Gender: One meta-analysis indicates that the efficacy of LAIV might be higher for vaccinated females than for vaccinated males; however, LAIV was reported as being superior in both genders (quantitative interaction). Age: For children aged 6 months to 6 years, a subgroup analysis of 4 studies showed consistent efficacy for LAIV over the analyzed age range. No studies were identified which address the issue of whether efficacy in the age range of <6 years is different from efficacy in the age range of 7-17 years. With regard to safety endpoints, two studies indicated that the safety and tolerance of LAIV in relatively young children, especially those under the age of 24 months, are inferior to those in older children (higher rate of acute wheezing / reactive respiratory tract disorders and all-cause hospitalizations). Region: Subgroup analysis indicated that the efficacy of LAIV was lower in studies conducted in the Asian area than in other regions.

Epidemiology
The observational studies evaluated in the epidemiological section were all conducted in the USA, in various general healthcare service settings, covering influenza seasons 1998/99 to 2009/10, usually investigating healthy children, although some of them also include children with chronic respiratory conditions, aged 18 months to 18 years, and in some cases other members of their households as well. Based on interventions LAIV was considered in each case in comparison with either TIV or non-vaccination. In terms of target parameters, avoidance of "acute respiratory illness" (ARI) and "medically attended acute respiratory illness" (MAARI) were mainly used in relation to effect, while "medically attended events" (MAE) and "serious attended events" (SAE) were used in relation to safety.

Effectiveness
With regard to direct protective effects, LAIV was reported to be effective in the prevention of influenza in children aged 1.5–18 years in the vast majority of evaluated epidemiological studies carried out under everyday conditions, as part of either general healthcare provision or school-based vaccination programs. The trend appears to indicate than LAIV is more effective than TIV. Apart from this direct protective effect for children themselves, indirect protective effects ("herd protection") were reported among non-vaccinated elderly population groups, even at relatively low vaccination coverage. An essential advantage of the epidemiological study of effect carried out by the Temple-Belton (T-B) research team is its duration over multiple influenza seasons within a study environment which can be regarded as relatively constant, with high numbers of participants. The 10%-20% risk reduction rates (RRR) determined by the T-B research team should therefore be regarded as a relatively robust expectation range.
Regarding indirect (“herd”) protective effects, these were shown for non-vaccinated elderly population groups in the evaluated studies, even at relatively low vaccination coverage among children as part of routine healthcare and vaccination programs. These effects are likely to be even higher at population level in conjunction with a possible general vaccination recommendation for children.

Safety

With regard to safety, LAIV generally can be considered equivalent to TIV in terms of both minor MAEs and SAEs, whereby the analysis of potential side effects was certainly very differentiated in individual studies. This also applies to use among children with mild chronically obstructive diseases.

Sociodemographic factors

With regard to sociodemographic factors influencing the effect and safety of LAIV there is information indicating that the vaccination of children reaches the highest intensity of effect at preschool age and then declines as age increases. With regard to gender, ethnic origin and comorbidity, on the other hand, there appears to be no relevant influence (socio-economic factors were scarcely taken into consideration and would anyway have been difficult to assess given the difference in healthcare service structure between the USA and Germany).

The methodological quality of all the included epidemiological studies was moderate. Consequently, there is a possibility of study results being biased, e.g. due to residual confounding or other methodology-related sources of error. This has to be taken into account when interpreting these studies.

Health economics

Although all the included studies generally deal with the economic evaluation of influenza vaccination in children, the studies address very different issues. The vaccination strategies to be evaluated mainly vary with regard to target age group, vaccine, vaccination setting, and the comparator used. The majority of studies analyze the cost-effectiveness of vaccinating children in comparison with non-vaccination, with very few undertaking a comparison of LAIV and TIV. In some cases the comparator is a situation with a low vaccination rate.

The majority of included studies were conducted for the USA, followed by studies originating from European countries and other parts of the world. Economic evaluation is usually undertaken from the perspective of the payer and/or society. Virtually all the studies are based on a decision-analytic model or contain individual modeling elements. While the six studies based on transmission models take into account the entire extent of indirect protective effects, nine studies only partially include indirect protective effects. This is usually based on an assumed additional protective effect for other members of the households of vaccinated children.

The majority of studies include an exclusive cost comparison, whereby monetary savings are also taken into account. Due to the short timeframe of many studies, it is not necessary to discount future costs or health effects. The vaccine prices used vary from study to study. All in all, vaccine costs are a critical factor impacting on cost-effectiveness. It was shown that a reduction in vaccine price can lead to a considerable improvement in cost-effectiveness.

The majority of studies arrive at cost-saving results in at least one scenario. In many studies, cost savings are achieved especially from a societal perspective. In some cases, however, consideration of indirect protective effects can also be identified as a driver of cost savings. Where studies fail to show cost savings, most studies at least deliver results that can be evaluated as highly cost-effective. Only a few studies show cost-effectiveness levels of over 10,000 EUR or USD per QALY. Some studies evaluate both the use of LAIV and the use of TIV, whereby LAIV emerges as the more cost-effective option.

Ethical, social and legal aspects

The efficacy of the vaccine, physicians' recommendations, and a potential reduction in influenza symptoms appear to play a role in the vaccination decision taken by parents/custodians on behalf of their
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children. Major barriers to the utilization of influenza vaccination services are a low level of perception and underestimation of the disease risk, reservations concerning the safety and efficacy of the vaccine, and potential side effects of the vaccine. For some of the parents surveyed, the question as to whether the vaccine is administered as an injection or nasal spray is also important. For this reason, effectiveness and method of administration might be assessed as being the most important properties of LAIV. Furthermore, there might be preference for LAIV over TIV among most children. The informative value of the study data is very limited on this issue, however, so studies should be carried out within the context of German healthcare services in order to be able to arrive at more significant conclusions.

All in all, it is evident that the approach of the physician in private practice and the availability of information appear to have a substantial influence on the vaccination decision taken by parents/custodians. The main source of information concerning influenza vaccines is the physician in private practice. Physicians’ recommendations therefore play a key role in the decision-making process.

Ethical conflicts are possible between child/parent self-determination and society's desire for general immunity. The issue as to whether children and teenagers can also be vaccinated against their parents' wishes should be weighed up in each individual case, taking the principle of proportionality into account, whereby interference in the decision-making rights of parents might increase the degree of risk to the child's well-being. The same also applies if vaccinations are to be prescribed by order, contrary to an individual's wishes - for the benefit of society or for the protection of vulnerable individuals. However, the risk to a child's well-being caused by influenza does not appear to be sufficient for a public debate as to whether seasonal influenza vaccination of children should be performed against the wishes of the child/parent.

Discussion

Age groups in the studies

The evidence concerning (clinical) efficacy of LAIV is available on a limited basis for children aged 7 to 17 years and additional studies would be desirable in this area, especially with children in the general population (i.e. without concomitant disorders as an inclusion criterion). One special focus might be an investigation as to whether efficacy/superiority can be proven across the entire age range (7 to 17 years) or whether there are signs of interaction with age.

Subgroup analyses indicate that LAIV was safe in children aged ≥24 months with mild/moderate asthma or wheezing in their case history, especially also relative to acute wheezing and hospitalizations with any cause. There are still no studies available for children with acute wheezing or children with severe asthma, however; additional studies would therefore be desirable in this risk population. The question as to whether tolerance of a LAIV vaccination can be improved in children aged 12 to 23 months relative to the occurrence of acute wheezing by different vaccination regimens (e.g. increasing dosage; first vaccination with TIV, followed by LAIV) might also be investigated by additional studies.

Transferability of study results

With regard to all considered areas, there are currently no data available for the German healthcare setting. Long-term direct and indirect effectiveness and safety should be supported by surveillance programs with a broader use of LAIV. The majority of studies were conducted in the USA. Whether the levels of vaccination effectiveness in the various age groups in children can be compared with each other is questionable because some studies have a relatively narrow age range while others tend to have a wide age range.

Influence of indirect protection effect

In the literature in general there seems to be consensus that a systematic vaccination of children contributes to a reduction of the burden of disease in higher age groups. However, the epidemiological
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studies identified dealing with this issue show methodological limitations that compromise the reliability of this statement.

Cost-effectiveness and access to immunisation

The majority of health economic studies evaluate the vaccination of children against influenza as a cost-saving or highly cost-effective intervention. The main influencing factors identified include choice of perspective, vaccine price, and consideration of indirect protective effects.

Beside this there is a need to conduct health economic studies to show the impact of influenza vaccination for children in Germany. Such studies should be based on a dynamic transmission model. Only those models are able to include the indirect protective effects of vaccination correctly.

The current situation regarding access to influenza vaccines in Germany should be debated critically. Particular aspects specific to health insurance companies should have no influence on the cost reimbursement of vaccinations recommended by STIKO. Apart from the reference price system, the discount contract system used extensively by the various health insurance companies must be called into question since there is a conflict of aims between cost savings for the group of insurance holders and a guaranteed supply of influenza vaccines. The supply bottlenecks also caused in this way have a detrimental effect on the high vaccination rates that are desirable in terms of health policy. Solely focusing on price as a decision-making criterion to the exclusion of quality and economy aspects is inappropriate. If certain vaccines should prove to have a protective effect in individual target groups, access should be granted with cost reimbursement. Since STIKO chiefly recommends LAIV for children aged 2 to 6 years, all individuals in this target group covered by statutory health insurance should be granted general access to services using LAIV.

Conclusion

In children aged 2 to 17 years, the use of LAIV can lead to a reduction in the number of influenza cases and the associated burden of disease. In addition, herd protection effects may be expected, especially among elderly age groups. However no data is available for the context of the German healthcare setting, so in the event of a broader use of LAIV, its long-term direct and indirect effectiveness and safety should be supported by further evaluation programs.

Since there is no general model available for the context of the German healthcare setting, statements concerning cost-effectiveness can only be made on a limited basis. In light of this aspect as well, health economic studies need to be conducted on the effects of influenza vaccination for children in Germany. Such studies should be based on a dynamic transmission model so as to be able to include the indirect protective effects of vaccination.

With regard to the ethical, social and legal aspects, physicians should discuss with parents the motivations for vaccinating their children and upcoming barriers for a broader vaccination coverage.

The present HTA provides an extensive basis for further scientific approaches and pending decisions relating to health policy.

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