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Cost-effectiveness of vaccination against cytomegalovirus (CMV) in adolescent girls to prevent infections in pregnant women living in France

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ABSTRACT

Background: CMV infections are the most frequent congenital infections worldwide.
Aim: Assess the cost-effectiveness of vaccination strategies of adolescent girls vs. current practice (hygiene counseling) to prevent CMV seroconversions during pregnancy in France.
Method: A Markov decision-tree model simulated overtime the trajectory of a single fictive cohort of 390,000 adolescent women aged 14 years old, living in France. Impact of vaccination was explored until the end of their reproductive live 40 years later.
Strategies compared: "S1: No vaccination" (current practice); "S2: Routine vaccination"; "S3: Screening and vaccination of the seronegative".
Model parameters: Seroconversion rate without vaccination (0.035%/pregnant woman-week); fetal transmission risk (41%). Vaccine vs. no vaccination: a 50% decrease in maternal seroconversions.
Outcomes: Quality-Adjusted Life-Years (QALYs) of the cohort-born babies; discounted costs; Incremental Cost-Effectiveness Ratio (ICER).
Results: S2 was the most effective strategy (with 35,000 QALYs gained) and the most expensive (€211,533,000); S1 was the least effective and least costly (€75,423,000). ICERs of strategy S3 vs. S1, and S2 vs. S3 were 6,000€/QALY gained (95% uncertainty range [2700–13,300]) and 16,000€/QALY [negative ICER (S3 dominated by S2) – 94,000] gained, respectively; highly cost-effective because ICER < 1∗ France's GPD/capita = €30,000.
Sensitivity analysis: If the seroprevalence was >62% (vs. 20% in the base case), S3 would become the most efficient strategy.

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Conclusion: In France, systematic vaccination of adolescent girls was the most efficient strategy to prevent maternal seroconversions. If the population was less than 62% immune, systematic screening and vaccination of susceptibles would become the most cost-effective approach.

1. Introduction

Cytomegalovirus (CMV) infections during pregnancy can cause congenital infections [1,2]. The incidence of congenital CMV infection is estimated at 0.2–2.2%/live births; the most frequent congenital infection worldwide [1]. After maternal seroconversions, a 41% fetal transmission risk occurs [3]. Of infected fetuses, 10–15% are born symptomatic [4] with newborns at high risk of developing permanent neurological or motor impairment, deafness, and blindness [2,4–6]. Among asymptomatic newborns, 5–10% will develop progressive hearing loss [7].

In France, around 50% of women of childbearing age are susceptible to CMV infection [8–12]. Between 2004 and 2005, the French national institute of public health conducted a national prospective study in metropolitan France to estimate the incidence of maternal CMV infection during pregnancy. It was found that 660–1600 seroconversions/100,000 pregnancies/year occur among CMV seronegative women having performed a serological screening to CMV infection leading to 150–270 newborns infected [13,14]. Routine serological screening of pregnant women is not recommended in France, given that health interventions after a diagnosed seroconversion are limited [13]. Nevertheless, it is estimated that 300,000 tests were performed nationally in 2004 [14].

Clinical trials on CMV vaccine are promising, with several candidates at different stages of testing [15]. In 2009, Pass et al. reported promising results from a Phase II trial on one candidate vaccine demonstrating around 50% (95% Confidence Interval (CI): [7–73%]) efficacy in preventing maternal primary infection in women after their first pregnancy [16]. Another randomized clinical trial in adolescent girls published in 2016 showed similar results (vaccine efficacy = 43%; 95%CI: [36–76%]) [17].

In this context, it is relevant to consider plausible vaccination approaches and their potential economic impact on French national health insurance. We conducted a model-based cost-effectiveness analysis to compare different CMV vaccination strategies of adolescent girls of 14 years of age living in France vs. the current practice (no CMV vaccination), and to identify the most efficient strategy in the French context.

2. Material and methods

2.1. Analytic overview

A Markov decision-tree model (Fig. 1) simulated the trajectory of one single fictive cohort of 390,000 adolescent girls, (i.e. the number of adolescent girls living in France in 2014). The model, build with TreeAge Pro©2014 (TreeAge Software, Inc., Williamstown, MA), followed-up the cohort from 14 years old during 40 years.

2.1.1. Markov model and trajectory

Several health states (Fig. 1B) were defined regarding CMV infection status (CMV seropositive/seronegative), pregnancy status (yes/no), and number of children (no/one/two children). Pregnancy states were also stratified based on CMV-related events (maternal seroconversion or not, leading to a congenital infection or not). A "death" state was also included. Because the course of the cohort was simulated during several decades, competitive mortality related to other causes than CMV was included. To allow women transitions between different states during the 40 years simulation period, a Markov process was included. At every time step, called a Markov cycle (fixed at 1 years), the women could progress to another health state (called Markov state), or remain in the same state if her status had not evolved.

The model simulated each woman's trajectory and included CMV infection occurrence in the general population, and/or during the first or second pregnancy. If a CMV infection occurred, the model considered its impact on the pregnancy, and its management if it was detected: maternal and fetal infection and their potential diagnosis, evaluation of fetal prognosis, presence or not of any impairment, spontaneous or medical medical termination of pregnancy (TOP). It also simulated the birth of infected or non-infected newborns, screening for potential sequelae, and neonatal care. The model finally included neonatal death or survival with or without sequelae, based on the infection status (symptomatic or asymptomatic) (Fig. 1C).

2.2. Strategies

Strategies compared were (Fig. 1A):

(i) S1: No vaccination (current practice); but application of guidelines on hygiene counseling to prevent CMV infections during pregnancy.
(ii) S2: Routine vaccination of all female adolescents aged 14 years old living in France in 2014. For this strategy, the vaccination schedule was assumed to be done by the general practitioner at the same time as HPV vaccination in France (3 doses at 0, 1, and 6 months). It was considered to be performed outside other French immunization programs (in order to be conservative toward the current practice).
(iii) S3: Routine screening and vaccination of the seronegative only. This strategy included a screening of all female adolescents aged 14 year old living in France. It consists on a serology testing the presence of CMV G antigen performed by a general practitioner. In this strategy only adolescents identified as seronegative with routine screening are vaccinated with the same schedule as in "S2: Routine vaccination".

2.3. Key assumptions

(i) Only maternal seroconversions after conception were considered. Preconception seroconversions and secondary maternal CMV infections were not included due to lack of consensual data.
(ii) Since the risk factor with the highest impact on seroconversion is "already having a child", we followed-up women until the birth of the second child [10,18,19]. Women could also have no child during the time of the simulation, or only have one child, based on French demographic data.
(iii) Adolescent women rather than adult women when they are about to be pregnant was preferred as the target population for vaccination. Indeed, we assumed that not all women plan a pregnancy, and that even those that plan do not visit health care providers before becoming pregnant.