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Matched case-control studies show impact of separate non-financial and financial encouragements on participation in voluntary Human Papillomavirus vaccination

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Conflicts of interest

FDS is an employee of the National Alliance of Christian Mutualities (NACM), the organizer of the first and co-organizer of the second encouragement campaign in the article. All authors declare that there are no conflicts of interest.

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The impact of separate non-financial and financial encouragements on participation in non school-based Human Papillomavirus vaccination : a retrospective cohort study

Abstract

Objective

Adolescent vaccination coverage under a system of non school-based vaccination is likely to be suboptimal, but might be increased by targeted encouragement campaigns. We analysed the effect on Human Papillomavirus (HPV) vaccination initiation by girls aged 12-18 of two campaigns set up in Flanders (Belgium) in 2007 and 2009: a personal information campaign and a combined personal information & financial incentive campaign.

Methods

We analysed (objective) data on HPV vaccination behaviour from the National Alliance of Christian Mutualities (NACM), Flanders' largest sickness fund. We used z-scores to compare the monthly proportion of girls initiating HPV vaccination over time between carefully selected intervention and control groups. Separate analyses were done for older and younger girls. Total sample sizes of the intervention (control) groups were 221 (243) for the personal information campaign and 629 (5,322) for the combined personal information & financial incentive campaign.

Results

The personal information campaign significantly increased vaccination initiation, with older girls reacting faster. One year after the campaign the percentages vaccination initiation for the oldest girls were 64.6 % and 42.8 % in the intervention and control group, respectively ($z = 3.35$, $p = 0.0008$); for the youngest girls the percentages were 78.4 % and 68.1 % ($z = 1.71$, $p = 0.09$). The combined personal information & financial incentive campaign increased vaccination initiation among certain age groups. One year after the campaign the difference in percentage points HPV vaccination initiation between intervention and control groups varied between 18.5 % ($z = 3.65$, $p = 0.0002$) and 5.1 % ($z = 1.12$, $p = 0.26$).

Conclusion

Under a non school-based vaccination system, personal information and removing out-of-pocket costs had a significant positive effect on HPV vaccination initiation, although the effect substantially varied in magnitude. Overall, the obtained vaccination rates remained far below those realised under school-based HPV vaccination.

Introduction

In Belgium, the quadrivalent and the bivalent HPV vaccines (Gardasil ® en Cervarix ®) were licensed in September 2006 and September 2007, respectively. On May 2nd, 2007 the Belgian Superior Health Council (SHC) recommended organized (school-based), free HPV vaccination for girls aged between 10 and 13 years. Despite this recommendation, only three years later, in September 2010, free school-based HPV vaccination (with the possibility to refuse vaccination or to be vaccinated by one's own physician) was introduced in Flanders (the northern region of Belgium, in which about 57 % of the Belgian population lives). Before that time, the HPV vaccine was only administered to girls during personal consultations by general practitioners and gynaecologists. Our data apply to this period of non school-based, non-free vaccination. It could be expected that, given the system's voluntary, non-free nature, HPV vaccination coverage would be suboptimal, especially among underprivileged groups [1, 2]. Therefore, extra encouragement actions were undertaken by different organizations to stimulate HPV vaccination. Here we investigate the effect of two such actions on HPV vaccination initiation.

In this introduction, we first outline the main characteristics of the system of non school-based, non-free HPV vaccination. Then, we provide more information on the encouragement actions. Finally, we summarize our research questions. A timeline with the most important events mentioned in this introduction can be found in Figure 1.

The system of non school-based, non-free HPV vaccination

Between November 2007 and September 2010 HPV vaccines in Flanders were only available via the system of non school-based, non-free vaccination.

The term *non school-based* implied that the girls themselves (potentially guided by their parents and / or physician) had to take the initiative to be vaccinated. They had to obtain a prescription for the vaccine from their physician, buy the vaccine at the pharmacy and go back to their physician three times to receive each of the recommended three doses of the vaccine.

The term *non-free* referred to the fact that, although during particular periods and for particular age groups partial reimbursement was provided, girls wanting to be vaccinated had to pay for it. The price of the vaccine was 130.22 euro per dose (for full vaccination 3 doses were required per girl). For girls eligible for partial reimbursement by the National Government, the out-of-pocket (OOP) cost was substantially lower. For most of them the OOP cost was 10.80 euros per dose. For girls with the so-called “BIR” statute (Beneficiary of Increased Reimbursement) the OOP cost was lower (7.20 euros per dose). Within the Belgian health insurance system, people from low-income households are assigned the BIR statute, and consequently pay lower co-payments. At the time of our analysis, there were two basic grounds for being assigned the BIR status. In both cases, a low household income was a direct or indirect condition: first, people receiving certain social benefits and their partners and descendants were automatically entitled to the statute. Second, certain other categories of people (most importantly orphans, widows, widowers, disabled, elderly, long term unemployed) were entitled to the statute after an income test had shown that their household income was below a certain threshold.

Before November 2007 girls wanting to start HPV vaccination had to pay the full price for the vaccine. The National Government provided partial reimbursement for girls aged 12-15 from November 2007 on, and for girls aged 12-18 from December 2008 on. Further, during the whole period the girls had to pay an OOP cost for the consultations with their physician to become vaccinated. For consultations at a general practitioner the OOP cost was 5.43 euros for non-BIR girls and 1.40 euros for BIR girls (fees as valid on January 1st 2007). Consultations at a gynaecologist were more expensive (7.24 euros for non BIR girls, 2.47 euros for BIR girls, with in some cases supplements charged by the gynaecologist).

The partial reimbursement of the HPV vaccines was organized through a third-payer arrangement with the sickness funds. Belgium has a system of compulsory health insurance, covering the entire population. Health insurance is organized through private, non-profit sickness funds. Membership of a sickness fund is compulsory, but the choice of sickness fund is free [3]. When girls, eligible for partial reimbursement, bought a HPV vaccine at their pharmacy, they only had to pay the OOP cost, with their sickness fund paying the rest of the

cost directly to the pharmacy. Afterwards, this sickness fund could claim the cost back from the national government.

Two encouragement actions

It is generally accepted that the best way to achieve high vaccination coverage, especially for underprivileged groups, is to offer school-based, free vaccination [1, 2].

The reasoning behind this is that under a system of non school-based, non-free vaccination certain system barriers will prevent people from starting (or completing) vaccination. First, girls mostly have to rely on collective information from media and word-of-mouth advertising when making their vaccination decision, and actively need to take a series of steps to become vaccinated. Studies have shown that informational letters, reminders or personal invitations can help to overcome this barrier [4, 5]. Further, studies have indicated that the existence of an OOP cost can pose a significant barrier to different preventive health behaviours and that removing this barrier can stimulate these same behaviours [6-8].

During the period of non school-based vaccination several organizations undertook actions to remove barriers associated with the system. By studying the effect of these actions we can assess whether and to what extent removing these barriers resulted in vaccination coverage rates similar to those obtained under school-based vaccination.

The first campaign we investigated was a *personal information* campaign. This campaign was organized by the National Alliance of Christian Mutualities (henceforth: NACM), the largest sickness fund in Flanders. It was launched when the National Government introduced partial reimbursement for the HPV vaccines in November 2007. The introduction of the HPV vaccines on the market and the start of partial reimbursement by the national government for girls aged 12-15 were widely advertised in the media. However, the NACM expected that some of the eligible girls would not be reached by the media campaigns, or would be too late. Therefore, in a letter, the criteria for partial reimbursement and the way to receive HPV vaccination were explicitly and personally communicated to girls approaching the maximum age for partial reimbursement.

The second campaign was a combined *personal information & financial incentive* campaign. This campaign was organized by the province of Flemish Brabant (one of the five provinces in Flanders) in cooperation with the NACM. It was launched some months after the National Government had widened the age criteria for partial reimbursement to girls aged 12-18. Although the OOP cost for the HPV vaccines after partial reimbursement was substantially lower than the full price of the vaccines, the province reckoned that for girls from low-income families it would still be too high. The encouragement consisted of a letter with information on the vaccine and the reimbursement rules. This letter also served as a voucher, worth the OOP cost for the vaccine. It was directed at girls with BIR status living in the province.

Research questions

To estimate the effect of the actions on HPV vaccination initiation we compared HPV vaccination initiation rates over time between carefully selected intervention and control groups that did or did not receive either of the encouragements. Our main research question was whether after the encouragement the percentage HPV vaccination initiation was significantly higher in the intervention groups than in the corresponding control groups. The obtained vaccination initiation rates could then be compared to those realized under the free, school-based system. Further, we also wanted to know whether the reaction of the girls depended on their age, as previous research had shown that under the system of non-organized vaccination, controlling for other factors, older girls tended to have a higher hazard of HPV vaccination initiation than younger [9].

Materials and methods

All data extractions and analyses were performed at the Medical Management Department of the NACM under supervision of a Social Security Physician.

Data

Data on HPV vaccination came from the reimbursement claims of the NACM. These contain information on all pharmaceuticals reimbursed to NACM members within the Belgian health insurance system. They can be considered a complete and objective source on HPV

vaccination behaviour by girls eligible for partial reimbursement, since partial reimbursement of the HPV vaccines was organized through a third-party arrangement with the sickness funds. When an eligible girl bought a HPV vaccine at the pharmacy, this purchase (and the accompanying reimbursement) was automatically registered in the reimbursement files. A disadvantage of working with reimbursement files was that they only contain information on *reimbursed* HPV vaccines. We thus did not have information on HPV vaccines purchased *before* the introduction of partial reimbursement by the national government. Because the number of vaccines sold before November 2007 was actually extremely small [10], in our analyses we assumed that the percentage HPV vaccination initiation before November 2007 was equal to zero.

Interventions

Personal-information campaign:

The campaign was launched on October 31st, 2007, the day before the national government introduced partial reimbursement for girls aged 12-15. It was targeted at a subgroup of the girls eligible for partial reimbursement, namely girls approaching their 16th birthday, who had the least time left to initiate HPV vaccination. More specifically, the letter was sent to all female NACM members born between November 16th 1991 and December 31st 1992. These girls had between 14 days and 14 months left before they would be no longer eligible.

The encouragement consisted of a letter that contained information on the rules for partial reimbursement. It was said that the full price of the HPV vaccine was 130.22 euros per dose. Girls of minimum 12 and maximum 15 years old only had to pay an OOP of 10.60 euros per dose (7.20 euros if they had been assigned the BIR status). The letter stressed that the partial reimbursement would only be granted if vaccination was initiated before the girls' 16th birthday. The letter was accompanied by a leaflet with information on HPV, cervical cancer and the role of the HPV vaccine in the prevention of cervical cancer.

Personal information & financial incentive campaign:

The personal information & financial incentive campaign was launched on February 6th 2009, some months after the national government had widened the age criteria for partial

reimbursement to girls aged 12-18. It was directed to a different subgroup of the girls eligible for partial reimbursement, namely those girls living in low-income households (with BIR statute). More specifically, it was targeted at the girls fulfilling the following criteria: living in Flemish Brabant, being assigned the BIR status and being born between January 1st 1992 and December 31st 1996. The encouragement consisted of a letter, sent by the NACM, which stated that the province of Flemish Brabant would bear the OOP cost for the HPV vaccine for girls who were minimum 12 and maximum 18 years old. It was explained that the girls had to obtain a prescription from their physician. With this prescription, together with the letter, they could get the HPV vaccine for free at their pharmacy. The upper half of the reverse side of the letter contained more information on HPV, cervical cancer and the role of the vaccine in preventing cervical cancer. On the lower half the girls had to write down the dates of purchase of the 3 doses of the HPV vaccine, each accompanied by a stamp from the pharmacy.

Evaluation framework

General evaluation framework

We aimed to study the potential differential effects of the campaigns in girls of different age groups using retrospective cohort data. For each age group we selected intervention and control groups that we assumed to be highly similar at population level (the selection criteria are outlined in detail below). Because of this assumed high degree of similarity no covariates had to be included in the analysis: we just compared HPV vaccination initiation rates over time between the intervention and control groups. Consequently, analyses of smaller groups became possible.

For the personal information campaign we performed one comparison for the oldest girls in the target group, and one for the youngest. For this campaign we only had information on HPV vaccination initiation rates *after* the campaign (*post-test only* design), since it was launched at the start of the partial reimbursement (and thus at the start of the registration of the HPV vaccines in the NACM's reimbursement claims).

For the combined personal information & financial incentive campaign we performed five separate comparisons, one per year of birth of the girls in the target group. Because the

campaign was launched much later, we had information on HPV vaccination initiation rates both *before* and *after* the campaign (*pre-test post-test* design).

Because a deliberate selection of adequate intervention and control groups was crucial to reduce the risk of bias, this selection is explained in detail below.

Personal information campaign

The campaign was targeted at the approximately 15,000 NACM member girls born between November 16th 1991 and December 31st 1992.

The fact that the personal-information campaign was such a large-scale campaign allowed us to base our selection of the intervention and control groups for both the oldest and the youngest girls in the target group on subtle differences in day of birth. In the intervention groups, we included girls with a date of birth just within the age eligibility criteria for the campaign. In the control groups, we included girls with a date of birth just outside these age eligibility criteria.

The oldest girls in the target group of the campaign were those born in the second half of November 1991. For these girls we defined the intervention group as all girls born on November 16th, 17th and 18th 1991 (received a letter, N = 96), and the control group as all girls born on November 13th, 14th and 15th (did not receive a letter, N = 152).

The youngest girls in the target group of the campaign were those born in December 1992. For these girls we defined the intervention group as all girls born on December 29th, 30th and 31st (received a letter, N = 125) and the control group as all girls born on January 1st, 2nd and 3rd 1993 (did not receive a letter, N = 91).

Personal information & financial incentive campaign

The campaign was targeted at the 629 girls who met the following criteria: living in Flemish Brabant, being assigned the BIR status and being born between January 1st 1992 and December 31st 1996.

Compared to the personal information campaign, the combined personal information & financial incentive campaign was organized at a much smaller scale. Therefore, all the girls targeted by the latter campaign were included in our analysis. For each birth cohort, the

intervention group consisted of the girls born in the selected year (between 1992 and 1996), living in Flemish Brabant to whom the BIR status had been assigned. The control group consisted of girls fulfilling the same criteria (born in one of the selected years and being assigned the BIR statute) but living in one of the other four provinces in Flanders (Antwerp, Limburg, West-Flanders, East-Flanders). The number of observations in each of the intervention groups was 150 (1992), 106 (1993), 136 (1994), 118 (1995) and 119 (1996), respectively. The number of observations in each of the control groups was 1,222 (1992), 1,130 (1993), 1,045 (1994), 969 (1995) and 956 (1996), respectively.

Note that the girls born in 1992 (both those in the intervention and those in the control group) also had been subject to the personal information campaign. We further comment on this in the Discussion.

Statistical analyses

The date of reimbursement of the first dose of a HPV-vaccine was retrieved from the reimbursement claims of the NACM. This date was converted into the month of reimbursement.

We made monthly comparisons of the cumulative proportion HPV vaccination initiation between the selected intervention and control groups. Our period of analysis ran from November 1st 2007 (when partial reimbursement was introduced) to August 31st 2010 (since from September 2010 school-based HPV vaccination was introduced). For each month we assessed whether the difference between the two proportions was significant (Z-score). The Effect Size (ES) [11-13] was used as a measure of the practical importance of the observed differences and was calculated as follows:

$$ES = \left| 2(\arcsin \sqrt{P1}) - 2(\arcsin \sqrt{P2}) \right|$$

with P1 and P2 the proportion of girls that started HPV vaccination in the intervention and the control group, respectively. The ES is a scale-free index that is independent of the sample size. As such it can be uniformly interpreted in different studies. The operational definitions for judging the practical importance of the results in the case of differences between proportions are: $ES \approx 0.20$: small ES, negligible practical importance; $ES \approx 0.50$: medium ES, moderate practical importance; and $ES \approx 0.80$: large ES, crucial practical importance [12].

Results

Personal information

The impact of the personal information campaign on HPV vaccination initiation is illustrated in Figure 2. The figure shows the difference in the cumulative proportion HPV vaccination initiation over time between intervention and control group for both the oldest girls in the target group (Panel A) and the youngest girls in the target group (Panel B).

The oldest girls in the target group (panel A) only had a very short time left (14 days) in which they could claim partial reimbursement of their vaccines by the National Government. For these girls, the strongest effect was found immediately after receiving the letter: 57.3 % of the girls in the intervention group initiated vaccination in November 2007, while in the control group only 30.9 % of the girls did ($z = 4.11$, $p = 0.0002$). This difference corresponded to an ES of 0.48. The ES then gradually decreased to reach a plateau at a value of about 0.42 between February 2008 and October 2008. From December 2008 onwards the age criteria for partial reimbursement were widened to girls aged 12-18. During that period the ES decreased again.

The youngest girls in the target group (panel B) still had more than 1 year left before their right to partial reimbursement by the National Government would expire (on their 16th birthday). For them, the strongest effect was found only 5 months after the letter had been received. While in November 2007 the difference in vaccination initiation between intervention and control group was only 3.2 percentage points (corresponding to an ES of 0.14) ($z = 0.59$, $p = 0.56$), this difference increased to 16.9 percentage points in April 2008 (corresponding to an ES of 0.33) ($z = 2.53$, $p = 0.01$).

Personal information & financial incentive campaign

Figure 3 shows the results of the personal information & financial incentive campaign on HPV vaccination initiation per year of birth. For clarity, confidence intervals have been omitted but they can be found in the appendix (Figure 4). Since the personal information & financial incentive campaign was launched some time after the partial reimbursement had been introduced we now had pre- and post-test measures of vaccination behaviour. Girls born between 1992 and 1995 all became eligible for partial reimbursement in November 2007 since at that moment they were between 12 and 15 years old. Hence, for each of these birth cohorts, the cumulative proportion HPV vaccination initiation started to rise from

November 2007 on. Girls born in 1992 were a special case, as they were reached by the personal information campaign as well. This caused a very high proportion HPV vaccination initiation from very early on. The curve for girls born in 1996 started to rise only in 2008, since these girls reached the minimum age for partial reimbursement eligibility (12) in the course of 2008. In January 2009, one month before the campaign was launched, the cumulative percentage HPV vaccination initiation for each of the birth cohorts in Flemish Brabant was 59 % (1992), 56 % (1993), 35 % (1994), 24 % (1995) and 10 % (1996). For most of the birth cohorts there were no significant differences in vaccination behaviour between intervention and control group at that time. Only for girls born in 1993 the proportion HPV vaccination initiation was slightly higher in the intervention group as compared to the control group (1992: $z = 0.4$, $p = 0.66$; 1993: $z = 2$, $p = 0.04$; 1994: $z = 0.4$, $p = 0.68$; 1995: $z = 0.5$, $p = 0.61$; 1996: $z = 0.5$, $p = 0.65$).

In February 2009 the personal information & financial incentive campaign was launched. As a result, for some of the birth cohorts we saw a sharp increase in HPV vaccination initiation in the intervention group as compared to the control group. For the oldest girls in the sample, those born in 1992, the pre-test HPV vaccination initiation proportion was already quite high. Their post-test vaccination behaviour did not significantly differ between the intervention and the control group (e.g. in April 2009 $z = 1.2$, $p = 0.21$). For the second oldest girls in the sample, those born in 1993, the pre-test vaccination behaviour was slightly higher in the intervention group. After the campaign, however, this difference between the intervention and the control group was much larger and highly significant (e.g. in April 2009 the cumulative proportion HPV vaccination initiation in intervention and control group was 67 % and 49 %, respectively, $z = 3.5$, $p = 0.0004$). For girls born in 1994 and 1995, the cumulative percentage HPV vaccination initiation in the intervention groups was slightly higher than that in the control group (e.g. in April 2009 for birth year 1994 48 and 41 %, respectively and for birth year 1995 36 and 30 %, respectively), but this effect was not significant ($z = 1.4$, $p = 0.15$ for birth year 1994 and $z = 1.3$, $p = 0.18$ for birth year 1995). For the youngest girls in the sample, the effect of the encouragement campaign was again significant: after the campaign, in April 2009, the proportion girls that had started HPV vaccination in the intervention group was 35 %, compared to 15 % in the control group ($z = 5.5$, $p < 0.0001$). The effect of the campaign (as indicated by the divergence between the curves of the intervention and control group) lasted for about 4 to 5 months. However, the

difference between the intervention and the control group persisted until the end of the observation period.

Discussion

Previous research has identified various interventions that can increase vaccination rates among children and adolescents [14-18]. Among these, implementing a school-based vaccine delivery strategy seems particularly effective [1, 2]. However, an interesting question is to what extent targeted encouragement actions can increase vaccination rates under a non school-based vaccination system. Studies on ways to encourage HPV vaccination still remain rare, especially studies that use actual behaviour as the dependent variable (two exceptions include e.g. [19, 20]). In this study we found that under a system of non school-based, non-free vaccination both personal information and removing the OOP costs significantly improved HPV vaccine uptake. The effect of the campaigns however substantially varied in magnitude and depended on the age of the girls.

Under the system of non school-based, non-free HPV vaccination in Flanders partial reimbursement was provided by the National Government. The introduction of this partial reimbursement was widely advertised in the media. In the present study we found that girls who were, on top of this media exposure, informed in a personal letter about their reimbursement conditions had a higher vaccination initiation rate than girls who were not. The final ES of receiving information personally was between 0.30 and 0.40, corresponding to a small to medium effect size [12]. The effect lasted for about 4 or 5 months, but caused a difference in vaccination initiation rates that persisted for a much longer period. Those girls who had only a short time left before their rights to partial reimbursement would expire reacted much faster to the campaign.

Under the system of non school-based HPV vaccination in Flanders, girls from low-income families had a lower chance of initiating HPV vaccination than girls from higher income families [9, 21]. We found that a combined personal information & financial incentive campaign, whereby low-income families (BIR girls) received information on the HPV vaccine and a voucher worth the OOP cost for the vaccine, increased the HPV vaccination rate for these girls. This effect lasted for about 4 to 5 months, but again the difference in vaccination initiation rates between intervention and control groups persisted for a much longer period. However, the effect was only significant for the oldest and the youngest girls in the target

group. In order to come to grips with this difference, it is important to realize that these girls were in a different situation at the moment the campaign was launched.

First, girls born in 1992 were a special case. They were reached by both the personal information and the personal information & financial incentive campaign. As the first campaign targeted all girls born in 1992, the vaccination initiation rates of both the intervention and the control group of the second campaign were already quite high at the start of this campaign. Although our results showed no effect of the second campaign for these girls, it is likely that we would have found an effect if no first campaign had been launched.

Girls born in 1993, 1994 and 1995 were all eligible for partial reimbursement by the government from the moment this reimbursement was introduced in November 2007. Hence, from November 2007 on the cumulative percentage vaccination initiation for these age groups steadily rose. In line with findings from earlier research, the (pre-intervention) increase was steeper for the oldest girls (those born in 1993), which might have been the result of the fact that parents of younger girls thought their daughter was too young to be vaccinated or chose to postpone vaccination [9]. The fact that we found a significant effect of the encouragement for girls born in 1993, but not for girls born in 1994 and 1995, might have been due to a similar age effect.

Girls born in 1996 were in a somewhat different situation. When partial reimbursement by the national government was introduced, these girls had not reached the minimum age for partial reimbursement yet. As such, the many media campaigns at that time were not aimed at them. Hence, the provincial encouragement campaign might have had an effect similar to the effect of the personal information campaign on girls born in 1992 in that it was the first information given on the vaccine to these girls at a moment they became eligible for partial reimbursement. Remarkably however, girls born in 1996 never reached a similarly high vaccination rate after the campaign as girls born in 1992. Again, other factors may have played a role in explaining the large effect of the personal information campaign for girls born in 1992, such as a sense of urgency created by stressing the approaching age limit for reimbursement and the fact that the girls targeted by the personal information campaign were already older when this campaign was launched.

A question remains which aspect of the combined personal information – financial incentive campaign (the informational or the financial) caused the observed differences in vaccination

behaviour. In this regard we note that before this campaign (in January 2009) for low-income girls born in 1992 the personal information campaign had already been capable of inducing a HPV vaccination initiation percentage of 60 %, even among this difficult to reach population. Although the combined personal information-financial incentive campaign further increased this percentage to 70 % it is plausible that when the campaign would only have consisted of information, this would also have caused a substantial increase in vaccination behaviour among other birth cohorts.

How should we evaluate the effect of the campaigns?

A first way is to compare the obtained vaccination initiation rates to those obtained under school-based vaccination. When school-based HPV vaccination was introduced in Flanders in 2010, the vaccination initiation rate immediately rose to 85.3 % in the first year of school-based vaccination [22]. It is therefore clear that non school-based vaccination, even if 'optimized' by targeted encouragement campaigns, was never nearly as effective as school-based vaccination in terms of the realised vaccination coverage. Thus, if governments decide – after carefully balancing health benefits and vaccination risks based on the available evidence – to recommend population-based HPV vaccination, a school-based delivery strategy is clearly much more effective. In view of the pivotal role sufficiently high vaccination coverage plays to achieve herd immunity, school-based HPV vaccination is likely more cost-effective than any form of the non school-based vaccination options in our study, from both the payer's and societal perspectives.

However, in cases where such school-based delivery strategy is not feasible, targeted encouragement campaigns might be envisaged. In such cases, the estimation of the incremental costs and benefits of setting up these campaigns can be a useful evaluation tool, too.

To evaluate the personal information campaign in terms of the costs, we calculated the total program costs with and without the campaign. The cost per vaccinated girl without any campaign was calculated as the sum of the price of 3 doses of the vaccine (390.66 euros) and the price of 3 GP consultations (54.3 euros), giving a total of 444.96 euros per vaccinated girl. The personal information campaign increased the costs with 0.59 euros (price of a stamp) per girl, regardless of her vaccination situation.

The size of the target population per year of birth was 15,000 girls. We take the vaccination coverage realized by November 2008 (1 year after the campaign) by girls born in 1992 as an example. Without the campaign the coverage was 68.1 % (Figure 2, panel B, control group), while with the campaign it increased to 78.4 % (Figure 2, panel B, intervention group). Hence, the total program costs increased from 4,545,266 euros without the campaign to 5,241,580 euros with the campaign. This corresponded to 450,69 euros per extra vaccinated girl. It is clear that the cost per extra vaccinated girl was only marginally higher than the initial cost per vaccinated girl in the absence of the campaign.

The personal information & financial incentive campaign also increased the program costs with 0.59 euros (price of a stamp) per girl, regardless of her vaccination situation. As we had no data on the extra administration costs associated with the campaign (the reimbursement of the OOP cost was administered by the financial department of the province), these could not be taken into account. Hence, the calculated costs of this campaign are an underestimation of the real costs.

The size of the target population was 629 girls. Taking the vaccination rates realised 1 year after the campaign (February 2010) as an example we see that among girls born in 1993 the campaign increased the vaccination coverage from 52.3 % to 70.6 %. Hence, the total program costs increased from 146,377 euros without the campaign to 197,966 euros with the campaign. This corresponded to 448.18 euros per extra vaccinated girl. For girls born in 1994, who responded far less to the campaign, the coverage 1 year after the campaign was 45.6 % without and 50.7 % with the campaign. The total program costs increased from 127,625 euros to 142,270 euros, corresponding to 456.5 euros per extra vaccinated girl. Again the cost per extra vaccinated girl was not much different from the cost per girl without the campaign. However, as administration costs were not taken into account, the extra costs for the personal information & financial incentive campaign are an underestimation of the real costs. Further, as the campaign entailed a reimbursement of the OOP costs, the distribution of the program costs between the government and the patients was shifted to the government.

The following limitations should be mentioned with regard to this study.

First, the encouragement actions were not set up according to a Randomised Controlled Trial (RCT) design. Although we paid attention to a careful selection of intervention and control

groups, we only had limited possibilities for testing the similarity between intervention and control groups, as the number of background variables in the NACM database was limited. Therefore, this similarity had to be assumed. We however think that this assumption is reasonable. For the personal information campaign girls were assigned to either the intervention or control group based on subtle differences in date of birth (just within, or just outside the age eligibility criteria for receiving the intervention, respectively). For the personal information & financial incentive campaign we had information on the pre-test vaccination behaviour of both the intervention and control group. In all but one comparisons there were no significant differences in pre-test vaccination behaviour between the intervention and control group. If there would have been important differences between the girls in the intervention and control group, these would likely also have affected the pre-test vaccination behaviour.

A second limitation is that in the case of the combined personal information – financial incentive campaign, we were not able to separate out the effect of information and the effect of the financial incentive. It was - in the words of Briss and colleagues - a multi-component action [17]. The inclusion of two different campaigns in our analysis however made it possible to put forward some hypotheses with regard to the possible drivers of the observed effects.

A third limitation is that we could not be completely sure that no other encouragement actions were undertaken during the same period. Thus we could not exclude potential bias, despite our media coverage assessments and extensive checks with the main stakeholders. However, we know for certain that none of the other Flemish provinces organized an encouragement campaign. Nineteen smaller towns and villages (out of 308) did, but the number of girls targeted was too small to significantly affect our results.

A fourth limitation is that we had no record on whether or not a girl actually received the encouragement letter. However, the Communication Department of the NACM confirmed us that less than 0.1 % of the letters did not reach the addressee.

Finally, as the personal information campaign was organized on such a large scale, social interactions between girls in the control and the intervention group might have decreased the difference in vaccination coverage between both groups. The possibility that girls in the control group were also influenced by the campaign was probably larger for the oldest girls in the analysis, who were all born in 1991, than for the youngest girls, who were born in

1992 (intervention) or 1993 (control). In Flanders the age of a girl in principle defines the grade in school – unless she has a school delay. Thus, the majority of girls in the same grade have the same year of birth. Hence, there will usually be more social interaction between girls of the same year of birth than between girls of a different year of birth, as has been shown by using social contact surveys [23].

Besides these limitations our analysis had several important strengths. First, while many other studies had to rely on the measurement of vaccination intentions, we were able to study the effect of the actions on actual vaccination behaviour. Second, because we worked with administrative data this measure of vaccination behaviour was not prone to the recall bias associated with subjective measures of behaviour. Third, we were able to study the effect of the actions over a long period of time.

Conclusion

Under a non school-based vaccination system personal information and financial incentives increased HPV vaccination initiation among girls aged 12-18. However, the effect substantially varied in magnitude and was limited to certain age groups. Overall, extra encouragement actions in the context of a non school-based system could not compete with a school-based vaccination system in terms of the obtained vaccination coverage. As implementing school-based vaccination is not always a feasible option, further research should shed light on the impact and cost-effectiveness of various encouragement strategies on (HPV-) vaccination behaviour under a non school-based system. Vaccination among girls from low income families deserves special attention in this context, as women from lower socioeconomic background have a higher chance of contracting cervical cancer, participate less in cervical cancer screening and tend to be reached less by health communication strategies. Our research suggests that the impact of encouragement strategies would be highest if personalized communication is used indicating relatively short timelines over which the eligibility for subsidized HPV vaccination runs. This needs to be confirmed in the context of different health care systems. Different encouragement approaches could also be tested using a randomized controlled trial or case-control design, overcoming some of the limitations of our study.

Figure captions

Fig 1 is a timeline with the most important events described in the introduction

Fig 2 illustrates the impact of the personal information campaign on HPV vaccination initiation for two groups: girls approaching the upper age limit for reimbursement eligibility (panel A, oldest girls) and girls still further from the upper age limit for reimbursement eligibility (panel B, youngest girls). It plots the cumulative percentage HPV vaccination initiation (with 95 % Confidence Intervals) over time between November 2007 and August 2010. In each panel vaccination rates are compared between an intervention group (who received the encouragement) and a control group (who did not receive the encouragement). The figure also shows the Effect Size (ES). All girls are members of the National Alliance of Christian Mutualities and live in Flanders (Belgium)

Fig 3 illustrates the impact of the personal information & financial incentive campaign on HPV vaccination initiation for girls from six years of births (each year of birth in a separate panel). It plots the cumulative percentage HPV vaccination initiation over time between November 2007 and August 2010. In each panel vaccination rates are compared between an intervention group (who received the encouragement) and a control group (who did not receive the encouragement). The figure also shows the Effect Size (ES). All girls are members of the National Alliance of Christian Mutualities and live in Flanders (Belgium)

Fig 4 is equal to Fig 3 but now with 95 % Confidence Intervals (these have been omitted in Fig 3 for clarity reasons)

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Introduction
Gardasil on Belgian
market

Sep 2006

Introduction
Cervarix on
Belgian market

Sep 2007

Partial reimbursement
girls aged 12-15

Nov 2007

Oct 2007

NACM Personal
information
campaign

Partial
reimbursement girls
aged 12-18

Dec 2008

Feb 2009

Flemish Brabant
Information-financial
incentive campaign

School-based HPV
vaccination

Sep 2010

Government actions

Other encouragement
actions

Figure title: Effect of personal information campaign on HPV vaccination initiation

Figure title: Effect of the personal information & financial incentive campaign on HPV vaccination initiation, by year of birth

Appendix: Effect of the information & financial incentive campaign on HPV vaccination initiation, with 95 % CI