

# School-based HPV Vaccination: Variation in Inter-school Vaccine Uptake not Influenced by the Introduction of a New Information Brochure

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## Abstract

**Background:** Switzerland, with an adolescent HPV vaccination coverage at 59%, remains far from reaching the crucial swiss national goal of 80% coverage. Our objective was to implement a new information brochure in schools to increase HPV vaccination uptake. **Methods:** We designed a public health quality project. A new information brochure was produced and was distributed to a test group of 9<sup>th</sup> grade students from the Canton of Vaud, in Switzerland during the 2019-2020 school year. Vaccine uptake of the test group was compared to those of all other students in 2019-2020 and of students in the same schools in 2017-2018. **Results:** 12,143 electronic records were analyzed. 713 students were enrolled in 6 schools where the new brochure was distributed. Median age was 13 years (IQR 12-13), and 6,031 (49.7%) were female. Vaccine uptake was 52% (6,299/12,143). The new brochure did not result in increased uptake. Age  $\geq$  13 years (aOR 1.39, 95% CI 1.22-1.58) was significantly associated with uptake. Uptake increased between 2017-2018 (51%, 3,216/6,307) and 2019-2020 (52.8%, 3,083/5,836,  $p=0.04$ ) due to increased acceptance among boys. The only determinant of uptake in 2019-2020 was uptake in the same schools in 2017-2018. **Conclusion:** The introduction of a new information brochure was insufficient to increase HPV vaccination coverage. More innovative strategies are needed.

**Keywords:** Human papillomavirus- HPV vaccines- preventive health services- vaccine uptake- vaccine hesitancy

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## Introduction

In May 2018, the Director-General of the World Health Organization (WHO) issued a call to action to eliminate cervical cancer within a few generations through widespread HPV vaccination, cervical screening, and early diagnosis. More recently, in November 2020, WHO officially launch the Global Strategy to Accelerate the Elimination of Cervical Cancer (World Health Organization, 2020).

Human papillomaviruses are small, nonenveloped DNA viruses that infect cutaneous and mucosal epithelia. High-risk genital HPV types cause most high-grade precancerous lesions and > 99.7% of cervical cancers (Frazer et al., 2006). Approximately 570,000 cervical cancers and 311,000 deaths occurred worldwide in 2018. HPV is also associated with other genital and oropharyngeal cancers and with anogenital warts.

Bivalent and quadrivalent HPV vaccines that contain antigens of HPV16 and HPV18, which cause at least 70% of cervical cancer, were licensed more than 10 years ago. These vaccines have high protective efficacy against infections and precancerous cervical lesions associated with these types (Arbyn et al., 2018). More recently, a nonavalent vaccine has also been licensed that protects against seven carcinogenic HPV types that, together, cause approximately 90% of cervical cancers (Joura et al., 2015). Quadrivalent and nonavalent vaccines also protect against HPV6 and HPV11 that cause 90% of genital warts (Frazer et al., 2006) (Frazer et al., 2006). With a high-performing cervical cancer screening system (HPV screening every 5 years instead of cytology every 2 years) and high vaccination coverage (82% of adolescent girls and 76% of 12-year-olds by 2017), Australia is on track to become the first country to eliminate cervical cancer (Hall et al., 2018). Assuming sustained high vaccine coverage and

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compliance with screening recommendations, a recent projection estimates that Australia could achieve cervical cancer elimination (threshold of 4 new cases per 100,000 women annually) within 20 years (Hall et al., 2018). Switzerland, with an adolescent vaccination coverage rate for 2 doses of 59% between 2017 and 2019, remains far from attaining this crucial goal (Office fédéral de la santé publique, 2020).

Since 2007, HPV vaccination has been recommended for teenage girls aged 11 to 15 years by the Swiss Federal Office of Public Health and is offered free of charge within the framework of cantonal programs (catch-up is possible up to the age of 26) (Office fédéral de la santé publique, 2008). In the Canton of Vaud, one of the 26 member states of the Swiss Confederation that has an independent administrative competence for the management of school immunization, Gardasil® quadrivalent vaccine has been offered in schools during the 9<sup>th</sup> year of compulsory schooling since 2008. HPV vaccination was also recommended for adolescent boys aged 11 to 15 in 2015, and was implemented in schools in the Canton of Vaud in 2016. School vaccine uptake was approximately 70% during the first year of implementation but fell steadily afterwards. The nonavalent vaccine Gardasil 9® has been available in Switzerland since the beginning of 2019 but was only introduced in Canton de Vaud schools during the 2019-2020 school year.

Our objective was to implement a new information brochure addressing potential parents' hesitations about HPV vaccination in the school environment, highlighting the latest WHO recommendations to increase the HPV vaccination rate in the Canton of Vaud. Having identified several elements in the current brochure (Office fédéral de la santé publique, 2019) that may raise suspicions of HPV vaccination, we believed that we could increase immunization coverage by improving communication regarding the benefits and safety of HPV vaccination through the creation of a new information document.

## Materials and Methods

### *Design, setting, and population*

We conducted a public health quality project in collaboration with the School Health Promotion and Prevention Unit (PSPS Unit: Unité de Promotion de la Santé et de Prévention en milieu Scolaire) of our canton. We tested a new brochure promoting HPV vaccination in schools in the Canton of Vaud. Ninth grade students (usual age of 12 years at the beginning and 13 years at the end of the school year) during the school years 2017-2018 and 2019-2020 and aged 11 years or older were eligible to participate. A test group (TG) received the new information brochure as part of the 2019-2020 cantonal vaccination program. Several control groups were created from pupils of the 2017-2018 and 2019-2020 vaccination campaigns. Control Group 1 (CG1) included students of the 2019-2020 school year who did not receive the new brochure. Control Group 2 (CG2) included students of the 2017-2018 school year attending the same schools as the TG. Control Group 3 (CG3) included students of the 2017-2018 school year who were

not included in CG2. We chose the 2017-2018 school year because many students were vaccinated outside of school to access Gardasil 9® during the 2018-2019 school year, and the details of these vaccinations were not available. The PSPS Unit identified the schools forming the TG (2019-2020) and CG2 (2017-2018) to be representative of the total population of the Canton of Vaud. Thus, three groups of schools were defined according to their immunization coverage during the year 2017-2018 (low, medium or high) and two schools from each group were selected to arrive at a total of six schools necessary to obtain the number of students calculated to form the TG (cf. Statistical analyses).

The receipt of a reply coupon duly signed by the parents attesting to the acceptance or non-acceptance of the vaccination was necessary for the inclusion of students in our statistical analyses. The distribution of this form was already part of the school vaccination program and according to the ethics committee, no further specific information related to our study, nor signature of a specific consent form, was required. This study was approved by the institutional ethics committee (CER: 2019-00482) as a public health project. The level of data anonymization obviated a requirement for written informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice, and Swiss regulatory requirements.

### *Intervention*

#### *Development of the new brochure*

The official Swiss brochure on cancer and genital warts due to HPV (Office fédéral de la santé publique, 2019) emphasizes the mode of viral transmission, and uses illustrations of flirting teenagers that may deter parents from consenting to the vaccination of their children. We deemed that the text does not emphasize the most important benefits of vaccination sufficiently. The text is also addressed primarily to teenagers, whereas we reasoned that the target audience should also include parents, because they are ultimately responsible for signing the consent form for vaccinations administered in schools. To improve the information document, we evaluated the content of brochures used in England, Wales, Scotland, Northern Ireland, Ireland, and Australia, and conducted a literature review to address the issue of vaccine hesitancy in our message. The content of this brochure has been validated by the PSPS Unit and by the Steering Committee for School Vaccination in the Canton of Vaud. The graphic form of the brochure was produced by the audiovisual service of Lausanne University Hospital (Service d'appui multimedia - SAM) (Figure 1, supplementary File 1).

#### *Vaccination procedure*

School nurses (and occasionally school physicians) inform 9<sup>th</sup>-grade students about vaccination in classrooms. They control the immunization status of all students, and offer the scheduled administration of recommended vaccinations (including HPV) and catch-up of missed vaccinations. They distribute a comprehensive information booklet on immunization, and on request by students, the official Swiss brochure on cancer and genital warts

caused by HPV. Students then receive a reply coupon to be signed by parents who are requested to indicate which vaccines they accept for their children. Teenagers return the form to the school nurse who immunizes them in conjunction with school physicians according to parental responses. Finally, the school nurses enter the students' vaccination information into a dedicated computer program. For adolescents in the TG, in addition to the comprehensive information booklet on immunization, our new brochure replaced the official Swiss brochure on HPV-related cancer and genital warts and was also sent by postal mail to their parents. The other steps remained unchanged.

*Statistical analyses*  
*Population size*

The proportion of students vaccinated in schools of the Canton of Vaud in 2017-2018 was 43%. Predicting a slight increase in coverage with the introduction of Gardasil®9, we projected a vaccination coverage of 45% without any change in vaccination procedures. By estimating a total population of students eligible for vaccination of approximately 8,000 and predicting an increase in vaccination coverage to 55% in our test group, we calculated that a minimum of 675 students in the test group would give us a power of 80% (level of significance was set at  $p < 0.05$ ) to demonstrate a 5% minimum difference in vaccination coverage.

*Analyses*

Vaccine uptake was our dependent variable. Gender, age, school establishment, school year, and exposure to our new brochure represented our 5 independent variables. Fischer and Kruskal-Wallis tests were performed for categorical and continuous values, respectively.

Multivariate analyses were performed to calculate adjusted odd ratios for potential determinants of vaccine uptake. Analyses were applied to our entire population and also separately for school years 2017-2018 and 2019-2020. All tests were bilateral (2-tailed), and a P value of  $\leq 0.05$  was considered statistically significant.

*Data collection*

Coded information for each participant was provided by the PSPS Unit (student number, age in years, HPV vaccine uptake, school year: 2017-2018/2019-2020, school establishment number, and grouping [TG, CG1, CG2 or CG3]). Specific information regarding classes and educational paths was not transmitted to ensure anonymity. Coding information was then immediately destroyed by the PSPS Unit to guarantee total anonymity.

**Results**

*Population characteristics and groupings*

We obtained 15,409 electronic files, representing 14,177 students enrolled in the 9<sup>th</sup> grade in 53 school establishments in the Canton of Vaud (Figure 2). After exclusion of 1,232 duplicate files and 14 files of children under 11 years old, 14,163 school children were eligible to participate. After excluding students with missing vaccine uptake data, 12,143 electronic records were analyzed (Figure 2). Seven hundred and thirteen students were enrolled in the 6 schools where the new brochure was distributed during the 2019-2020 school year. The remaining 11,430 students represented the 3 control groups (CG1=5,123, CG2=624, GC3=5,683). The median age of our population was 13 years (IQR 12-13), and 6,031 (49.7%) were female.



Figure 1. New HPV Vaccination Information Brochure

Table 1. Determinants of Vaccine Uptake - Univariate Analyses

Determinant	Vaccine uptake, n/total (%)		
	Total population 6299/12143 (52)	School year 2017-2018 3,216/6,307 (51)	School year 2019-2020 3,083/5,836 (52.8)
<b>Gender</b>			
F	3,163/6,031 (52.5)	1,654/3,145 (52.6)	1,509/2,886 (52.3)
M	3,136/6,112 (51.3)	1,562/3,162 (49.4)	1,574/2,950 (53.4)
p-value	0.2	0.01	0.41
<b>Age category</b>			
> 13 ans	611/1,033 (59.2)	358/598 (59.9)	253/435 (58.2)
≤ 13 ans	5,688 /11,110 (51.2)	2,858/5,709 (50.1)	2,830/5,401 (52.4)
p-value	<0.001	<0.001	0.02
<b>School year</b>			
2019-2020	3,083/5,836 (52.8)		
2017-2018	3,216/6,307 (51)		
p-value	0.04		
<b>New brochure</b>			
Yes	368/713 (51.6)		368/713 (51.6)
No	5,931/11,430 (51.9)		2,715/5,123 (53)
p-value	0.89		0.49
<b>Vaccine uptake of school establishments in 2017-2018</b>			
<40%			851/1,932 (44.1)
40-50%			1,117/1,999 (55.9)
>50%			1,115/1,905 (58.5)
p-value			<0.001

### Determinants of vaccine coverage

Overall vaccine uptake was 52% (6,299/12,143), and the new brochure did not contribute to its increase (Table 1). During the 2019-2020 school year, 51.6% (368/713) of TG accepted the vaccination in comparison to 53% (2,715/5,123) of CG1 ( $p=0.49$ ) (Table 1). The comparison of vaccine coverage between TG (51.6%; 368/713) and CG2 (50.2%; 313/624) also showed no significant difference ( $p=0.6\%$ ). In the entire study population, gender distributions were similar among those who accepted or refused the vaccination. However, there was a significant difference in the 2017-2018 school year, when adolescent boys (1,562/3,162; 49.4%) were significantly less likely than adolescent girls (1,654/3,145; 52.6%) to accept vaccination. Vaccine uptake was also proportionally higher among older adolescents in both of the studied school years. Altogether, 59.2% (611/1,033) of the students 13 years of age or older accepted the vaccination compared to 51.2% (5,688/11,110) of younger students ( $p<0.001$ ). Vaccine uptake was also higher in 2019-2020 (52.8%; 3,083/5,836) than in 2017-2018 (51%; 3,216/6,307,  $p=0.04$ ). Finally, we found a significant correlation between school vaccine uptake rates in 2017-2018 and in 2019-2020. The vaccine uptakes in 2019-2020 among students in schools with <40%, 40-50% and > 50% vaccine uptake in 2017-2018, were 44% (851/1,932), 55.9% (1,117/1,999) and 58.5% (1,115/1,905), respectively ( $p<0.001$ ).

Our multivariate analyses showed that the 2019-2020

school year (aOR 1.09, 95% CI 1.01-1.17) and being 13 years of age older (aOR 1.39, 95% CI 1.22-1.58) remained significantly associated with vaccine uptake. The increased vaccine uptake between studied school years was due to a greater increase in immunization coverage among boys. While the vaccine uptake rate in adolescent girls remained stable (52.6% in 2017-2018 and 52.3% in 2019-2020), it increased from 49.4% to 53.4% in adolescent boys between 2017-2018 and 2019-2020, becoming similar to the vaccine uptake in females. Thus, male gender was significantly associated with a lower probability of being vaccinated in 2017-2018 (aOR 0.87, 95% CI 0.78-0.96) but not in 2019-2020 (Table 2). School vaccine uptake in 2017-2018 was the only predictor of vaccine uptake in 2019-2020 (Table 2).

### Discussion

Our results show that our new information brochure aimed at improving communication regarding the benefits and the safety of HPV vaccination did not increase vaccine uptake among 9<sup>th</sup> grade students in the Canton of Vaud. We have highlighted the significant impact of the school environment on immunization coverage. We have also noted a school-year effect with increased vaccination coverage in 2019-2020 that can be explained by an increased uptake in adolescent boys.

Our findings suggest that the simple revision of written information is not enough. Because our brochure

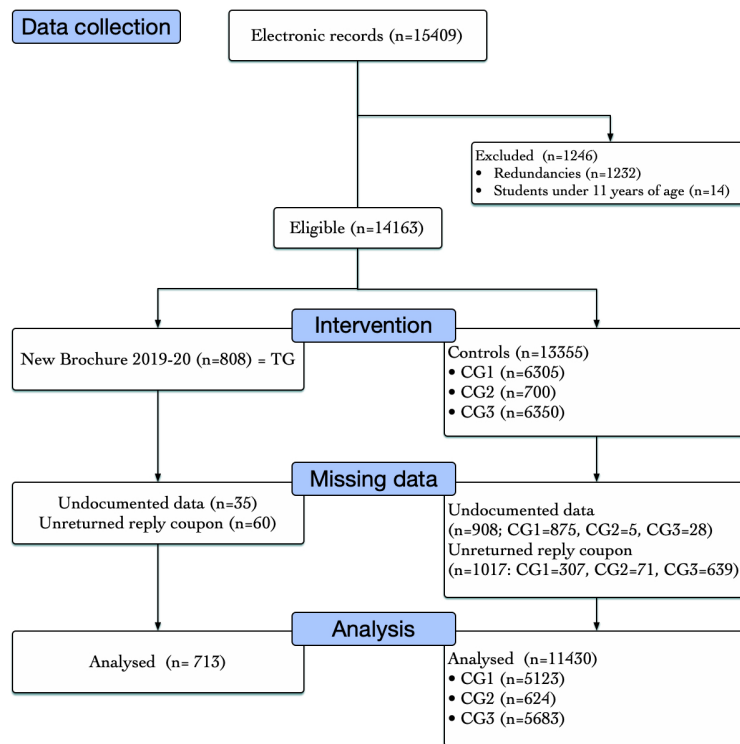


Figure 2. Flow-chart of Inclusion and Group Assignment. TG, test group (9th-grade students from 6 schools in school year 2019-2020); GC1, control group 1 (9th-grade students from all the other school establishments in school year 2019-2020); GC2, control group 2 (9th-grade students from the same schools as TG in school year 2017-2018); GC3, control group 3 (9th-grade students from all other schools of the Canon of Vaud in school year 2017-2018)

has not decreased immunization coverage, we do not believe that its content or form should be questioned. It was inspired primarily by the brochure used in Australia, where vaccination coverage is very high. In a Cochrane review, 3 studies (1 randomized clinical trial and 2 cluster-randomized trials) in which vaccination information and education were offered to adolescents and their parents showed increased vaccine uptake with an overall relative effect of 1.43 (95%CI 1.16-1.76) (Abdullahi et al., 2020). However, in comparison to our study, the interventions in these 3 studies incorporated

educational programs that included either audio-visual support or face-to-face instruction with the adolescents or their parents. The use of more complex measures is therefore certainly necessary to increase vaccination coverage.

Although we did not demonstrate an impact of our brochure, our study generated several interesting findings. The first is the significant association between schools and vaccination coverage. Unfortunately, the data in our possession do not allow us to identify these variables in our population, but we can hypothesize that socio-economic

Table 2. Determinants of Vaccine Uptake - Multivariate Analyses

Characteristic	Adjusted odds Ratio (95%CI) for vaccine uptake	p-value
All population		
Age > 13 years old	1.39 (1.22-1.58)	<0.001
Male gender	0.95 (0.88-1.02)	0.13
Brochure	0.95 (0.88-1.02)	0.54
School year 2019-2020	1.09 (1.01-1.17)	0.02
School year 2017-2018		
Age > 13 years old	1.5 (1.27-1.79)	<0.001
Male gender	0.87 (0.78-0.96)	0.006
School year 2019-2020		
Age > 13 years old	1.19 (0.97-1.45)	0.09
Male gender	1.04 (0.94-1.16)	0.83
2017-2018 school vaccine uptake*		
40-50%	1.6 (1.41-1.82)	<0.001
>50%	1.78 (1.57-2.03)	<0.001
Brochure	0.95 (0.81-1.11)	0.5

\*Comparator, <40% vaccine uptake; 95% CI, 95% confidence interval

and cultural factors, or the school nurses' promotion attitudes could very well explain this observation, as has been demonstrated in other settings (Baumann et al., 2019).

We also observed a significant increase in vaccination coverage between 2017-2018 and 2019-2020. The training of school nurses and of some of the school physicians regarding vaccination was strengthened in 2019 and may have improved vaccination promotion messages and thus vaccination coverage as a consequence of a better educational program. Indeed, as stated above, education added to vaccination information has been shown to improve vaccine uptake (Abdullahi et al., 2020). Another factor could be the introduction of the new Gardasil 9® vaccine as early as January 2019 in the Canton of Vaud, because the improved coverage of oncogenic strains strengthens the incentive for vaccination. However, a better understanding of the benefits of vaccination in boys, possibly related to the reinforcement of the message conveyed by school nurses not only in relation to their role as HPV vectors, but also as beneficiaries of disease prevention, probably played a significant role, as evidenced by a greater increase in vaccination coverage essentially in boys between 2017-2018 and 2019-2020. A Swiss cross-sectional interview based study explored HPV vaccination hesitancy in adolescents and young adults. While they showed that the odds for being unvaccinated was higher for hesitant females, this was not the case for males. To explain these results, they argue that other factors such as HPV vaccine awareness and knowledge may play a role, which certainly has been improved recently in our setting (Kiener et al., 2022).

Our study has several limitations. First, we note the lack of information on the extent of the reading of our booklet by parents. It could be hypothesized that the booklet may have had a positive impact in the families in which it was actually read. That said, the findings of our study reflect real life and can hardly be challenged by this argument. Second, high numbers of students were excluded because of either missing data or failure to return the reply coupon. An impact on the reliability of our results cannot be excluded. Third, our hypothesis estimating a potential difference in immunization coverage of 10% was too ambitious, as most interventions seldom produce an increase of more than 5%. Thus, our study did not have the statistical power to demonstrate a smaller difference in coverage. However, because we measured very similar vaccine coverage rates between groups, increasing the size of the TG would probably not have changed our statistical results. Fourth, our study was not randomized, and the intervention could not be blinded. However, we do not believe that these limitations had a significant impact on our results, as the information content was the same in all of the classes of the same schools. Fifth, we were able to obtain very little information to assess the impact of other potential determinants of immunization coverage (such as socio-economic data, or parental educational level). Sixth, we did not have out-of-school immunization data. We estimate that these immunizations could represent an additional 10% of vaccinations. The impact of our brochure on these vaccinations is therefore unknown.

Finally, we can criticize the method we used to develop our brochure. We based our approach on brochures used in different socio-cultural contexts and on a review of the literature. The approach advocated by the WHO consists rather in identifying the target populations and, through targeted interviews, in isolating the sources of vaccine hesitancy to be addressed in the promotional message of vaccination (World Health Organization, 2017).

To increase immunization coverage, it is necessary to adapt the message delivered in our brochure after identifying the determinants of parental vaccine hesitancy in our socio-cultural context and to establish one or more alternative strategies. An educational program that incorporates more than just written information might be necessary (Abdullahi et al., 2020). However, we believe that this effort has already been made and could explain the increased immunization coverage between 2017-2018 and 2019-2020. Other avenues of improvement should therefore be explored. Organizing catch-up vaccination campaigns among older adolescents, at compulsory school in higher grades or after the end of compulsory schooling, and improving the rate of return of reply coupons by sending reminders to parents, could facilitate increased vaccine uptake. Recent US data showed a higher likelihood of vaccination with a provider recommendation and in case of a well-child visit at 11-12 years, among other factors (Chen et al., 2021). This a strong argument for primary care physician involvement. Thus, a robust involvement of office-based pediatricians and other primary care physicians as well as family planning centers and pharmacists in providing initial or catch-up vaccinations should also be promoted.

We conclude that more ambitious strategies are required to achieve a greater global impact. The first impressions of mothers regarding HPV disease and vaccination of their children are often primal and influenced by exposures to social media (Baumann et al., 2019). Although the use of this information channel seems therefore essential, message content is also very important. Communication aimed at both the mind and the heart is more effective. This can be done on social networks by associating scientific facts with personal stories (Loft et al., 2020). Recent data demonstrating the precipitous decline in cervical cancer incidence attributable to the vaccine will be extremely valuable for scientific messaging (Lei et al., 2020). Thus, a campaign to promote HPV vaccination through a national public health policy that leverages media and acts on social networks should be prioritized.

Our study showed that the simple intervention of introducing new information material was insufficient to increase HPV vaccination coverage among 9<sup>th</sup> grade students in the Canton of Vaud. The increased immunization coverage in 2019-2020, after a trend of declining annual uptake rates since 2008, is nevertheless reassuring, and is explained by an increased vaccine uptake in adolescent boys. However, more innovative strategies will be needed to reach the swiss national goal of 80% coverage.

## Author Contribution Statement

Laurel Froidevaux: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Visualization, Funding acquisition. Cristina Fiorini-Bernasconi: Methodology, Data curation, Writing - Review & Editing, Funding acquisition. Valérie Campiche: Methodology, Data curation, Writing - Review & Editing, Funding acquisition. Mario Gehri: Supervision, Writing - Review & Editing. Martine Jacot-Guillarmod: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Funding acquisition. Pierre Alex Crisinel: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Funding acquisition, Project administration

All the authors (Laurel Froidevaux, Cristina Fiorini-Bernasconi, Valérie Campiche, Mario Gehri, Martine Jacot-Guillarmod, Pierre Alex Crisinel) declare that they have no competing interest related to this article

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### Availability of data

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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