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# Promotion de la santé sexuelle et de la vaccination contre le papillomavirus en collège à La Réunion

Phuong Lien Tran

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**Promotion de la santé sexuelle et de la vaccination contre le  
papillomavirus en collège à La Réunion**

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**Par **Phuong Lien TRAN****

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# Valorisation des travaux

## A. PUBLICATIONS DANS DES REVUES INTERNATIONALES

- Septembre 2020 Human papillomavirus genotyping on Reunion Island: A cross-sectional study of stored tissue samples.  
Eur J Obstet Gynecol Reprod Biol. 2020 Sep;252:294-299. doi: 10.1016/j.ejogrb.2020.07.001  
Tran PL, Zafindraibe N, Ah-You N, Fernandez C, Arrivets A, Gérardin P, et al.
- Février 2022 HPV vaccination hesitancy in Reunion Island.  
J Gynecol Obstet Hum Reprod. févr 2022;51(2):102277. doi: 10.1016/j.jogoh.2021.102277  
Tran PL, Bruneteaux A, Lazaro G, Bertolotti A, Boukerrou M.
- Juin 2022 Impact of a Papillomavirus Vaccination Promotion Program in Middle School: Study Protocol for a Cluster Controlled Trial.  
JMIR Res Protoc. 13 juin 2022;11(6):e35695. doi: 10.2196/35695  
Tran PL, Chirpaz E, Boukerrou M, Bertolotti A
- PROM SSCOL – Impact of a Papillomavirus vaccination promotion program in middle school to raise vaccinal coverage in Reunion Island.  
Vaccines, accepté nov 22, Vol 10, Issue 11,  
DOI : 10.3390/vaccines10111923  
Tran PL, Chirpaz E, Boukerrou M, Bertolotti A
- Understanding barriers and motivations to Papillomavirus vaccination in a middle school in Reunion Island.  
Eur J Obstet Gynecol Reprod Biol. (soumis)  
Tran PL, Leruste S, Sitthisone J, Humbert M, Gilhard X, Chirpaz E, Boukerrou M, Bertolotti A.
- Communication tools to address HPV vaccination with adolescents.  
J Health Commun (soumis)  
Tran PL, Chirpaz E, Castermann J, Leger R, Vallerian A, Bertolotti A, Boukerrou M.

## B. COMMUNICATIONS ORALES

- Janvier 2020 Paris Santé Femmes, Paris  
« Génotypage du papillomavirus à la Réunion
- Mai 2022 Paris Santé Femmes, Paris  
« Impact d'un programme de promotion de la vaccination anti HPV en milieu scolaire »
- Novembre 2022 ONCOTOM, 11<sup>e</sup> congrès de cancérologie des départements et régions d'outre-mer, La Saline, la Réunion  
« L'épidémiologie du cancer du col à la Réunion & Etude PROM SSCOL – vaccination HPV en milieu scolaire (bus santé)
- Novembre 2022 3<sup>e</sup> congrès de la recherche en santé de l'Océan Indien, St Leu, La Réunion  
« Impact d'un programme scolaire de promotion de la santé sexuelle et de la vaccination anti HPV »

## C. POSTERS

Novembre  
2022

3<sup>e</sup> congrès de la recherche en santé de l'Océan Indien, St Leu, La Réunion

« Efficacité présumée de la vaccination anti papillomavirus à la Réunion, via un génotypage sur des échantillons de tissus stockés »

« Freins à la vaccination anti HPV à l'île de la Réunion »

# RESUME

## Contexte

A La Réunion, le cancer du col de l'utérus est la troisième cause de cancer chez la femme. La prévention primaire repose sur la vaccination contre le papillomavirus (HPV). Une étude sur frottis et biopsies cervicales à La Réunion, montrait que les HPV les plus fréquents sur l'île étaient le HPV 16, 31, 51, 52, pour la plupart contenus dans le vaccin nonavalent contre le HPV (Gardasil 9). Ainsi 96,8% des lésions auraient pu être évitables par la vaccin. Cependant à La Réunion, le taux de couverture est faible (12,2%). Les principaux freins retrouvés auprès des mères d'adolescentes et de médecins généralistes, étaient le manque d'information et une méfiance envers les vaccins. L'objectif de l'étude était d'évaluer l'impact d'un programme de promotion de la santé sur la couverture vaccinale contre le HPV.

## Méthodes

Dans cette étude interventionnelle prospective et contrôlée de supériorité, un collège intervention où le programme de promotion a eu lieu, a été comparé à un collège témoin où aucune intervention spécifique n'était prévue, au cours de l'année scolaire 2020-2021, au Sud de La Réunion. Le programme combinait : information des élèves (cours magistraux, information personnalisée dans la cour de récréation, campagne de santé publique créée par les élèves), des parents, des médecins généralistes, vaccination gratuite à l'école (dans un " bus santé " garé dans la cour de l'école) avec le vaccin nonavalent contre le HPV.

## Résultats

A la fin de l'année scolaire, la couverture vaccinale était significativement augmentée dans le collège où l'intervention a eu lieu. Le mode de communication le plus efficace pour augmenter l'acceptabilité de la vaccination parmi les élèves, était la méthode participative, où les élèves étaient acteurs dans la création d'une campagne de santé publique. Cependant le faible taux de participation aux campagnes vaccinales pouvait être expliqué par la crainte d'effets indésirables graves par manque d'informations et de connaissances, la méfiance, et le tabou lié à la sexualité et aux grossesses chez les mineures, privant les enfants d'un dialogue avec leurs parents sur le sujet.

## Conclusion

La mise en œuvre d'un programme de promotion de la santé et l'offre d'une vaccination gratuite en milieu scolaire ont permis d'augmenter la couverture vaccinale. Ces résultats sont prometteurs et peuvent constituer un tremplin pour étendre ce programme à l'ensemble de l'île de La Réunion et espérer un jour diminuer le poids du cancer du col de l'utérus.

# ABSTRACT

## Background

In Reunion Island, cervical cancer is the third leading cause of cancer in women. Primary prevention is based on vaccination against papillomavirus (HPV). A study on cervical smears and biopsies in Reunion showed that the most frequent HPV on the island were HPV 16, 31, 51, 52, mostly contained in the nonavalent HPV vaccine (Gardasil 9). Thus 96.8% of lesions could have been prevented by the vaccine. However, in Reunion Island, the coverage rate is low (12.2%). The main obstacles found among mothers of adolescents and general practitioners were lack of information and vaccine mistrust. The objective of the study was to evaluate the impact of a health promotion program on HPV vaccination coverage.

## Methods

In this prospective, controlled superiority interventional study, a promotion program took place in a middle school, which was compared to a control school where no specific intervention was planned, during 2020-2021 school year, in the south of Reunion Island. The program combined: information for students (lectures, personalized information in the school yard, public health campaign created by students), parents, general practitioners, free vaccination at school (in a "health bus" parked in the school yard) with the nonavalent HPV vaccine.

## Results

At the end of school year, vaccination coverage was significantly increased in the school where the intervention took place. The most effective communication method to raise acceptability of vaccination among students was the participatory method, where students were actors in the creation of a public health campaign. However, the low participation rate in vaccination campaigns could be explained by the fear of serious adverse effects due to lack of information and knowledge, mistrust, and the taboo related to sexuality and pregnancy among adolescents, depriving children of a dialogue with their parents on the subject.

## Conclusion

Implementation of a health promotion program and free vaccination in schools increased vaccination coverage. These results are promising and are a stepping stone towards the extension of this program to the entire island of Reunion ; and hopefully someday the burden of cervical cancer may be reduced.



# ABREVIATIONS

|            |  |
|------------|--|
| ANSM       | Agence Nationale de sécurité du médicament                   |
| ARS        | Agence régionale de santé                                    |
| CCU        | Cancer du col de l'utérus                                    |
| CIN        | Néoplasie cervicale intra épithéliale                        |
| COVID      | Coronavirus  |
| CRCDC      | Centres régionaux de coordination des dépistages des cancers |
| FCU        | Frottis cervico utérin                                       |
| HPV        | Human papillomavirus   |
| IST        | Infection sexuellement transmissible                         |
| OMS        | Organisation Mondiale de la Santé                            |
| ORS        | Observatoire régional de la santé                            |
| PA         | Personne année   |
| PROM SSCOL | Promotion de la santé sexuelle en collège                    |
| REP        | Réseau d'éducation prioritaire                               |
| TIS        | Taux d'incidence standardisé                                 |



# I. INTRODUCTION

## A. EPIDEMIOLOGIE

D'après l'OMS, le cancer du col de l'utérus (CCU) est le quatrième cancer le plus fréquent chez la femme dans le monde, avec environ 570 000 nouveaux cas et 311 000 décès en 2018 (1).

En 2018 en France, le nombre de nouveaux cas dépistés de CCU est de 2920 avec un taux standard d'incidence (TIS) de 6,1 par 100 000 PA (personnes-années). Le pic d'incidence de la maladie est observé à 40 ans avec un âge médian et un âge moyen au moment du diagnostic respectivement de 51 et 56 ans (2).

A La Réunion, le TIS en 2017 est de 9,7 pour 100 000 PA, en diminution par rapport à 2000 où il était de 17,2/100 000 PA, mais tout de même deux fois plus élevé que dans certaines régions de France métropolitaine.

Sur l'île, le cancer du col représente la troisième cause de cancer chez la femme après le cancer du sein et du colon et est le huitième plus meurtrier avec un taux de mortalité standardisé de **4,8/100 000 PA en 2011 (contre 1,7/100 000 en métropole)** (3).

## B. HISTOIRE NATURELLE

Les papillomavirus humains (Human PapillomaVirus HPV) sont responsables de la plus fréquente des infections sexuelles transmissibles d'origine virale. Environ 45 génotypes HPV peuvent infecter la sphère ano-génitale et parmi les génotypes à haut risque, les HPV 16 et 18 ont un potentiel oncogène important et seraient responsable de 71 à 82 % des cancers infiltrants du col. Ils peuvent aussi être responsable de cancers du vagin, de la vulve, de l'anus, du pénis, et des voies aérodigestives supérieures (cavité orale, oropharynx, amygdales). En général, les infections à HPV sont transitoires : dans 60 à 80% des cas, l'infection est éliminée. Mais parfois, les modifications cytologiques et histologiques du col induites par HPV - répertoriées selon la classification de Bethesda - peuvent persister et évoluer progressivement vers un carcinome infiltrant. Le cancer du col de l'utérus est un cancer d'évolution lente; il met en moyenne dix à quinze ans à se former (4).

## C. PREVENTION

La prévention des cancers HPV-induits repose sur la vaccination anti HPV (prévention primaire). Pour le cancer du col de l'utérus, la prévention secondaire repose sur le traitement des lésions repérées par le dépistage par le Frottis Cervico-Utérin (FCU) ou test HPV. Toutefois, il n'y a pas de dépistage microbiologique réalisé pour le moment pour les cancers du pénis, de l'anus et de l'oropharynx.

Pour ce qui concerne le dépistage par le FCU, on est passé d'un dépistage individuel à un dépistage organisé en 2018. Les données issues des études ayant porté sur des départements pilotes pour ce qui concerne la mise en place du dépistage organisé ont montré que le taux de couverture, assez variables d'un département à l'autre, atteignait difficilement les 70% (5); cela conforte la nécessité d'y associer la vaccination comme stratégie complémentaire.

Un vaccin anti-HPV nonavalent est disponible en France actuellement depuis 2018 (Gardasil 9 ®, ciblant HPV 6, 11, 16, 18, 31, 33, 45, 52 et 58). L'HPV se transmettant essentiellement par voie sexuelle, il est important que les adolescents soient vaccinés avant le début de leur vie sexuelle. Il est ainsi recommandé de proposer la vaccination en ciblant les adolescents, âgés de 11 à 14 ans avec un rattrapage possible entre 15 et 19 ans pour les adolescents non encore vaccinés (6).

Cependant, la couverture vaccinale en France de 37,4% (schéma complet) en 2021 (7) est très inférieure à l'objectif de 60% qui était fixé à l'horizon 2019 dans le cadre du plan cancer 2014-2019, ce qui ne permet pas d'offrir une protection optimale de la population française vis-à-vis des affections induites par les papillomavirus.

Pourtant, la vaccination HPV a fait la preuve de son efficacité sur la prévalence du portage de l'HPV, mais aussi sur l'incidence des condylomes ou des dysplasies de grade intermédiaire (8,9). Ainsi, en Australie, où le taux de vaccination anti HPV est de près de 80%, ils prévoient que l'incidence standardisée du CCU passera sous la barre des 4 nouveaux cas pour 100 000 PA dès 2035 grâce à l'action combinée de la vaccination et du dépistage (10).

Seuls les niveaux de couverture élevés permettent d'obtenir une immunité de groupe. En comparaison à la situation actuelle, en France, une augmentation de couverture vaccinale jusqu'à 85% permettrait d'éviter a minima, par cohorte annuelle de femmes de 14 ans, 2 546 conisations (réduction du risque de 26%), 2 347 lésions précancéreuses CIN2/3 diagnostiquées (réduction du risque de 31%), 377 CCU (réduction du risque de 32%), 139 décès par CCU (réduction du risque de 39%) (11).

Les niveaux de couverture vaccinale élevés sont obtenus dans les pays qui vaccinent dans les écoles (12–14). D'après la méta-analyse réalisée par Perman et al (15), la réussite des programmes de vaccination scolaire repose sur leur direction et gouvernance, les modèles organisationnels et les relations institutionnelles, la capacité et les rôles de la main-d'œuvre, en particulier en ce qui concerne l'infirmière scolaire, la communication avec les parents et les élèves, y compris les méthodes pour obtenir leur consentement, l'organisation et la prestation des services cliniques.

Depuis décembre 2019, il est recommandé de vacciner aussi bien les filles que les garçons selon les mêmes modalités (6). Cela permettrait de favoriser l'immunité de groupe (« herd immunity ») et de diminuer la circulation du virus dans la population (16). En effet, les résultats de différents modèles mathématiques ont suggéré que la vaccination anti HPV universelle sans tenir compte du sexe (« gender-neutral »), apporterait un bénéfice incrémentiel, incluant la quasi élimination des verrues génitales et le portage des génotypes d'HPV présents dans les vaccins, aussi bien chez les hommes que chez les femmes (8). La vaccination chez les garçons peut être justifiée aussi par le fait qu'il n'existe pas de dépistage pour les cancers de l'anus, du pénis et de l'oropharynx.

Ainsi, le Haut Conseil de Santé Publique (HCSP), au regard de l'ensemble de ces données épidémiologiques, conseillait en 2014 la généralisation du dépistage organisé associée à la mise en place de modalités d'administration de la vaccination permettant d'atteindre un pourcentage élevé d'enfants, indépendamment de leur niveau social :

- l'adjonction d'une offre vaccinale en milieu scolaire (telle que le Royaume-Uni et l'Australie l'ont mise en place) permettrait d'atteindre cet objectif ;

- l'abaissement de 11 ans à 9 ans de l'âge de la vaccination pourrait être recommandé si cette mesure était susceptible de favoriser la mise en place d'un tel programme. Ce type de modalité est appliqué avec succès au Québec.

A La Réunion, le taux de couverture vaccinale contre le HPV est le plus de faible de France. Il est estimé par Santé Publique France à 12,2% chez les filles âgées de 16 ans en 2021 (7). Pourtant, le génotypage de HPV présents à La Réunion (17) (Article 1) montrait une haute prévalence de HPV 16, 31, 33, 51, 52 dans les lésions cervicales dysplasiques, et les cancers du col de l'utérus. Ces génotypes sont tous inclus dans le vaccin Gardasil 9 ®, soit 96,8% des lésions retrouvées qui auraient pu être évitables grâce à la vaccination HPV.

Ce faible taux de couverture à La Réunion a possiblement plusieurs explications. En premier lieu, les réunionnais et leurs médecins généralistes semblent peu informés sur l'existence de ce vaccin et pour ceux qui le connaissent, restent méfiants (18) (Article 2). En effet, d'après le dernier rapport de l'Observatoire Régional de la santé Océan Indien (ORS) sur les « connaissances, opinion et comportements de la population réunionnaise à l'égard de la vaccination » (19), seuls 5,4% des 1100 adultes interrogés ont spontanément cité l'existence de la vaccination HPV. De plus, les taux de couverture vaccinale dépendent du niveau socio-économique de la population, les taux les plus bas étant observés dans les populations les plus défavorisées. Ainsi, C. Blondel et al. décrivaient des taux de couverture pour la vaccination HPV plus faibles dans les populations bénéficiaires de la couverture maladie universelle complémentaire (CMU-C – maintenant appelée complémentaire santé solidaire) par rapport aux non bénéficiaires (20). Or, La Réunion est un des départements français avec les plus forts taux de pauvreté. Enfin, il existe à La Réunion une importante défiance vis-à-vis de la vaccination en général, et de la vaccination contre le HPV en particulier, chez les patients comme chez les médecins. Ainsi, toujours selon le rapport ORS sus-mentionné, 41% des réunionnais sont défavorables à certaines vaccinations, le vaccin anti HPV étant parmi le vaccin le plus souvent cité. Parmi les patientes non vaccinées contre le HPV, 37% déclarent que le vaccin ne leur avait pas été proposé par leur médecin. 7,3% ont été confrontées aux doutes exprimés par leur médecin concernant la vaccination en général, sachant que

89,3% des Réunionnais déclarent avoir confiance en leur médecin généraliste. Or, une revue systématique réalisée à partir de 79 études dans 15 pays (21,22) a montré que le facteur influençant le plus la vaccination HPV était la recommandation par le médecin. Aussi, les interventions ciblant les professionnels de santé, et surtout les médecins généralistes, paraissent donc primordiales, notamment quand elles sont combinées à des interventions ciblant la population à vacciner (23).

Ainsi, eu égard à la situation épidémiologique à La Réunion (incidence et mortalité élevées pour le CCU, taux de couverture par la vaccination HPV très bas), et en considérant les recommandations du HCSP de 2014, il nous est apparu intéressant d'étudier l'impact d'un programme de promotion de la santé sexuelle et de prévention des infections sexuellement transmissibles (IST) dont les pathologies liées au papillomavirus, avec un programme de promotion de la vaccination anti HPV chez les jeunes élèves scolarisés au collège.

## **Article 1.** Génotypage du papillomavirus à La Réunion : étude sur tissu congelé

Résumé :

Objectif : Nous avons souhaité illustrer et évaluer la prévalence et le schéma de distribution des génotypes du HPV cervical sur l'île de La Réunion, un territoire français d'outre-mer, dans le but de guider les futures politiques de vaccination.

Méthodes : Entre janvier 2008 et juillet 2012, les dossiers des femmes subissant un examen gynécologique ont été évalués rétrospectivement au CHU de La Réunion. Les critères d'inclusion étaient les suivants : biopsies du col de l'utérus avec diagnostic histopathologique de lésions de haut grade ou de cancer et résultats de frottis ASCUS (cellules malpighiennes atypiques de signification indéterminée). Le test INNO-LIPA HPV Genotyping Extra1 a été utilisé pour le génotypage du HPV.

Résultats : Au total, 401 frottis ASCUS et 94 biopsies cervicales ont été analysés, dont 162 frottis et 63 biopsies étaient positifs à l'ADN HPV (40,4 % et 67 % respectivement). Des ventilations détaillées de la distribution spécifique des génotypes HPV ont rapporté la prévalence des HPV 16, 31, 33, 51 et 52. Sur les 63 biopsies positives au HPV, 61 (96,8 %) contenaient au moins un génotype de HPV contenu dans le vaccin 9-valent contre le HPV. La fraction supplémentaire évitable des infections à HPV qui aurait pu être ajoutée par le nouveau vaccin 9-valent au vaccin bivalent actuel a été estimée à 26,2 %.

Conclusions : La vaccination avec le vaccin 9-valent devrait être efficace et, à long terme, pourrait réduire l'incidence du cancer du col de l'utérus à La Réunion. Néanmoins, les taux et la couverture vaccinale doivent être maintenus et améliorés.





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Full length article

## Human papillomavirus genotyping on Reunion Island: A cross-sectional study of stored tissue samples



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### ABSTRACT

**Objective:** We aim to illustrate and evaluate the prevalence and distribution pattern of cervical human papilloma virus (HPV) genotypes on La Réunion Island, a French overseas territory, with the aim to guide future vaccination policies.

**Study design:** Between January 2008 and July 2012, files of women undergoing gynaecological examination were retrospectively evaluated at the University Hospital, Reunion Island. Inclusion criteria required cervical biopsies with histopathological diagnosis of high-grade lesions or cancer and ASCUS Pap Smears (atypical squamous cells undetermined significance) results. The INNO-LIPA HPV Genotyping Extra<sup>®</sup> test was used for HPV genotyping.

**Results:** A total of 401 ASCUS Pap Smears and 94 cervical biopsies were analyzed, of which 162 smears and 63 biopsies were HPV DNA positive (40.4% and 67% respectively). Detailed breakdowns of HPV genotype-specific distribution reported prevalence of HPV 16, 31, 33, 51 and 52. Of the 63 HPV-positive biopsies, 61 (96.8%) contained at least one HPV genotype that is contained in the 9-valent HPV vaccine. The incremental preventable fraction of HPV infections that could have been added by the new 9-valent vaccine to the current bivalent vaccine was estimated at 26.2%.

**Conclusions:** Immunization with 9-valent vaccine should be effective, and in the long term, may reduce cervical cancer incidence in Reunion Island. Nevertheless, vaccination rates and coverage need to be maintained and improved.

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### Background

Cervical cancer is the second most frequent solid neoplasm in woman. It is the fourth leading cause of cancer-related mortality

worldwide, accounting for 266,000 deaths yearly [1]. Cervical cancer is commonly associated with a persistent Human Papillomavirus (HPV) infection, which induces cervical cell abnormalities that progress towards cervical carcinogenesis.

There are more than 100 genotypes of HPV, of which 13 are classified as high-risk drivers of cancer in humans [2]. HPV 16 and HPV 18 are the most commonly detected genotypes in human cancers (70%) across the world [3,4]. Of note, oncogenic nature of HPV genotypes is known to differ regionally, as influenced by socio-cultural and economic levels.

Cervical cancer fortunately is still one of the most preventable types of cancer. In France, three vaccines have been licensed against HPV and current recommendations target young girls aged

**Abbreviations:** ADK, adenocarcinoma; ASCUS, atypical squamous cells undetermined significance; CIN, cervical intra epithelial neoplasia; DNA, deoxyribonucleic acid; HPV, human papillomavirus; HR, high risk; LR, low risk; QIAGEN, QIAamp DNA FFPE Tissue Kit; SCC, squamous cell carcinoma.

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between 11 and 14. The most commonly used vaccine protects against high-risk HPV genotypes 16 and 18 [2]. More recently, a 9-valent HPV vaccine has been made available in France. In addition to the precedent, this also protects from HPV 6, 11, 31, 33, 45, 52, and 58 types.

In Reunion Island (RUN), a French overseas territory located in the Indian Ocean, standardized incidence and mortality rates were 10.8 and 4.8 per 100 000 women respectively, twice higher than figures observed in Metropolitan France [5]. RUN population is multiethnic and reflects four centuries of colonization, mainly from Europe, Madagascar, Africa and Asia (India and China). Given the diversity of population groups and constant migration flows, RUN is at the crossroad of HPV mix. As such, determining HPV genotypes that are associated with cervical cancer incidences on the island would have implications regarding primary prevention by vaccination.

In this study, we aim to describe prevalence and distribution pattern of HPV genotypes from abnormal Pap smears with ASCUS (atypical squamous cells undetermined significance) cytology and in biopsies of high-grade lesions and cervical cancers in RUN. To date, data on HPV prevalence and genotype distribution is limited. We seek to investigate associations and potential impact of the frequency of genotypes and the severity of the lesions to guide future vaccination policies. Vaccination coverage on RUN among girls aged 11–14 was previously reported to be just 9.8 % [6], thus improving vaccination coverage is crucial in this population.

## Methods

### Population and tissue samples

From January 2008 to July 2012, we selected all cervical biopsies with a diagnosis of high-grade lesion (cervical intra epithelial neoplasia CIN grade 2–3 or in situ carcinoma) or invasive cervical carcinoma, diagnosed within the histopathology laboratory, at the University Hospital, RUN. In addition, we also analysed all ASCUS Pap Smears from January 2011 to February 2012 diagnosed in one private histopathology laboratory of RUN. PAP smears were conventional cytology. Once ASCUS was diagnosed, patients were asked to come for another consultation. Another cervical sample was performed with Digene specimen transport medium. This liquid-based cytology, offered the possibility for HPV testing.

### DNA extraction

For cervical biopsies, sections of 5–10  $\mu\text{m}$  were realized using a microtome, from the paraffin blocks. DNA was extracted from resulting material using QIAamp DNA FFPE Tissue Kit (QIAGEN) following manufacturer's instructions, and stored at  $-80\text{ }^{\circ}\text{C}$ .

### HPV genotyping

For cytological samples (ASCUS Pap smears), HPV DNA detection was performed using Hybrid Capture 2 test. Samples were analysed for the presence of 5 low-risk (LR) HPV types (6, 11, 42, 43, and 44) and 13 high-risk (HR) HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). This enzyme linked immunoabsorbent assay is based on a sandwich hybridization followed by a non-radioactive alkaline phosphatase reaction with chemiluminescence in microplates. Samples containing more than 200'000 DNA copies of viral genome ( $>2\text{ pg/mL}$ ) with semiquantitative Hybrid Capture test, were subsequently analyzed for HPV genotyping.

Concerning histological samples (cervical biopsies), INNO-LIPA HPV Genotyping Extra<sup>®</sup> was used for HPV genotyping. This amplification kit detects and genotypes 28 HPV genotypes,

including 18 high-risk HPV (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82), 7 low-risk HPV (6, 11, 40, 43, 44, 54, 70), and 3 other unclassified HPV (69/71, 74).

This multiplex PCR-based (polymerase chain reaction) assay is followed by reverse line blot hybridization. Part of the L1 region of the HPV genome is amplified using SPF10 primers, and resulting biotinylated amplicons are then denatured and hybridized with specific oligonucleotide probes. An additional primer pair is added to monitor sample quality and extraction (human HLA- DPB1 gene). All probes are immobilized as parallel lines on membrane strips. After hybridization and stringent washing, streptavidin-conjugated alkaline phosphatase is added, which binds to any biotinylated hybrid previously formed. Incubation with a chromogen yields a purple precipitate and results can be visually interpreted.

### Statistical analyses

Data were collected using the software EpiData. Proportion of HPV genotypes within the different samples was expressed as the proportion of women positive for a given genotype among the total of HPV-positive samples.

Specific HPV genotypes might play a more dominant role in lesion development than others when multitype infections are observed. We postulate that the probability of a particular HPV genotype detected in a multitype ( $\geq 2$ ) infection, to be attributed to cancer, is equivalent to the positivity rate of this particular type among HPV-positive cases infected with a single infection.

Thus, multitype infections were added to single types in accordance with a proportional weighting attribution. For example, if five biopsies were found positive for both HPV 16 and HPV 33, of which 20 cases infected by HPV16 as a single type and four cases infected by HPV33 as a single type, then  $[5 \times 20 / (20 + 4)]$  or 4.17 of these two-multitype infected lesions would be attributed to HPV16 and  $[5 \times 4 / (20 + 4)]$  or 0.83 attributed to HPV 33 [7,8].

### Ethics

This study was approved by the local ethical committee and the National Commission for Informatics and Liberty, the French Data Protection Authority. All participants provided their informed consent for this study.

## Results

A total of 401 ASCUS Pap Smears and 94 cervical biopsies were analysed (Fig. 1).

Of 401 ASCUS Pap Smears analysed, overall prevalence was 40 % (162) within the study period. Higher prevalence of HPV infections (32 %) were identified in women aged between 25 and 35 years and mean age was 35.4 ( $\pm 12.3$ ) years. Of the 162 HPV-positive ASCUS Pap Smears, genotyping was possible for 100 samples, among which, 203 infections were described. There were 40 samples (40 %) positive with a single HPV genotype, whilst a multitype infection (2 or more) was found in 60 % of the samples: two genotype infections in 28/100 smears and three infections in 32/100 smears (Table 1). Most frequently detected genotype was 51HR (12.3 %), followed by types 31HR (10.3 %), 52HR (8.9 %) and 16HR (8.4 %). HPV 51 (20.7 %), HPV 16 (13.2 %), and HPV 52 (12.4 %) were the most commonly found in positive ASCUS Pap Smears. Fourteen women were concerned with low-risk HPV, HPV 44LR was the most frequently represented (6.9 %).

When we analysed percentages of prevalence of at least one of the HPV genotypes present in the 9-valent HPV vaccine, 70 % of women would be eligible recipients.

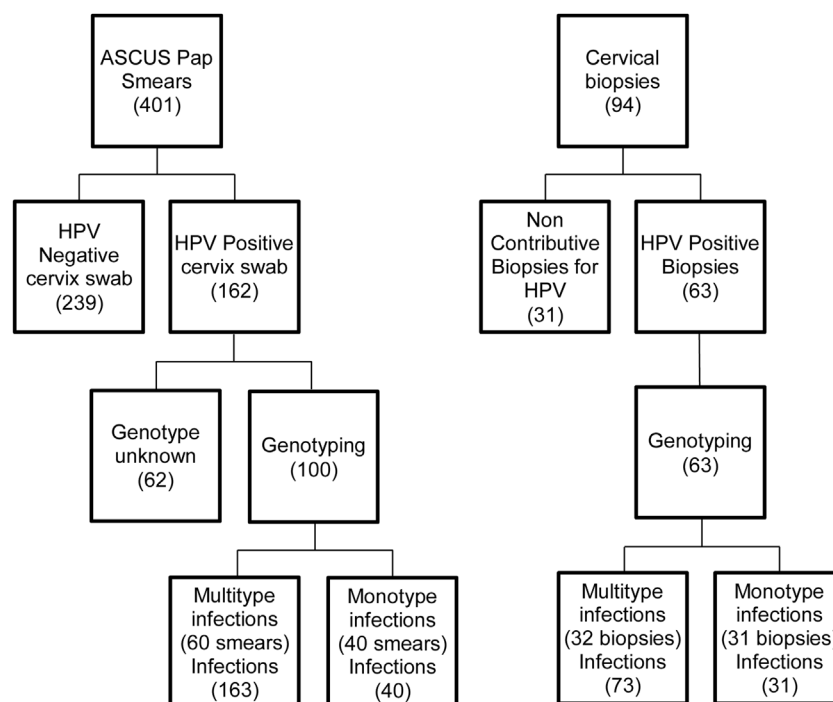


Fig. 1. Distribution of the samples analyzed for human papillomavirus genotype, La Réunion Island, 2008-2012.

Table 1

Distribution and contribution of HPV genotypes in 100 positive ASCUS Pap Smears, La Réunion Island, 2011-2012.

|                | HPV genotypes        | Unique (n = 40) | Double (n = 56) | 3 or more (n = 107) | Total (n = 203) n(%) | Contribution (% mean ± SD) |
|----------------|----------------------|-----------------|-----------------|---------------------|----------------------|----------------------------|
| High risk      | 16                   | 6               | 4               | 7                   | 17 (8.4)             | 13.2 ± 0.2                 |
|                | 18                   | 2               | 3               | 4                   | 9 (4.4)              | 4.4 ± 0.3                  |
|                | 26                   | 0               | 0               | 1                   | 1 (0.5)              | 0                          |
|                | 31                   | 1               | 7               | 13                  | 21 (10.3)            | 9.8 ± 0.4                  |
|                | 33                   | 3               | 0               | 5                   | 8 (3.9)              | 5.0 ± 0.4                  |
|                | 35                   | 0               | 1               | 1                   | 2 (1.0)              | 0                          |
|                | 39                   | 0               | 2               | 2                   | 4 (2.0)              | 1.6 ± 0.5                  |
|                | 45                   | 1               | 1               | 4                   | 6 (3.0)              | 1.7 ± 0.4                  |
|                | 51                   | 9               | 7               | 9                   | 25 (12.3)            | 20.7 ± 0.2                 |
|                | 52                   | 6               | 2               | 10                  | 18 (8.9)             | 12.4 ± 0.3                 |
|                | 53                   | 2               | 6               | 2                   | 10 (4.9)             | 6.3 ± 0.3                  |
|                | 56                   | 0               | 2               | 6                   | 8 (3.9)              | 0                          |
|                | 58                   | 1               | 6               | 7                   | 14 (6.9)             | 8.0 ± 0.4                  |
|                | 59                   | 0               | 1               | 1                   | 2 (1.0)              | 0                          |
|                | 66                   | 5               | 2               | 7                   | 14 (6.9)             | 9.2 ± 0.3                  |
|                | 68                   | 2               | 3               | 3                   | 8 (3.9)              | 6.1 ± 0.3                  |
| 73             | 0                    | 2               | 1               | 3 (1.5)             | 0                    |                            |
| 82             | 1                    | 0               | 3               | 4 (2.0)             | 1.7 ± 0.4            |                            |
|                | HPV X – undetermined | 1               | 0               | 0                   | 1 (0.5)              | 1.0                        |
| Low risk       | 6                    | 0               | 1               | 1                   | 2 (1.0)              | 0                          |
|                | 11                   | 0               | 0               | 0                   | 0 (0)                | 0                          |
|                | 40                   | 0               | 0               | 1                   | 1 (0.5)              | 0                          |
|                | 43                   | 0               | 0               | 3                   | 3 (1.5)              | 0                          |
|                | 44                   | 0               | 3               | 10                  | 13 (6.4)             | 0                          |
|                | 54                   | 0               | 1               | 0                   | 1 (0.5)              | 0                          |
|                | 70                   | 0               | 1               | 0                   | 1 (0.5)              | 0                          |
| Not-classified | 69/71                | 0               | 1               | 5                   | 6 (3.0)              | 0                          |
|                | 74                   | 0               | 0               | 1                   | 1 (0.5)              | 0                          |

HPV : human papillomavirus.  
SD: standard deviation.

Of the 94 cervical tumour biopsies, HPV DNA genotyping was viable for 63 samples (67%). In this group, mean age of the patients was 48.6 (± 17.1) years.

Of the 63 positive cervical biopsies, the most commonly detected histologic type was squamous cell carcinoma, with 38 cases (60.3%),

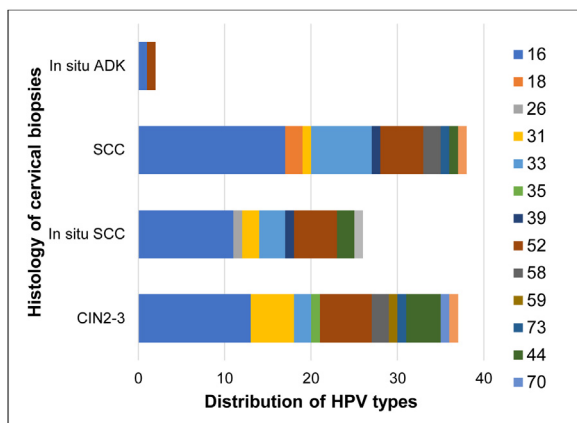
followed by CIN2–3 (cervical intraepithelial neoplasia) and in situ carcinoma, with 37 (58.7%) and 26 (41.3%) cases, respectively. There were two biopsies of in situ adenocarcinoma.

Unique genotype HPV infections were detected in almost half (31/63) of the positive samples, whilst the other half (32/63) were

**Table 2**  
Distribution and contribution of HPV genotypes in 63 cervical biopsies, La Réunion Island, 2008–2012.

|                | HPV genotypes | Unique<br>(n = 31) | Double<br>(n = 44) | 3 or more<br>(n = 29) | Total<br>(n = 104)<br>n(%) | Contribution (% mean ± SD) |
|----------------|---------------|--------------------|--------------------|-----------------------|----------------------------|----------------------------|
| High risk      | 16            | 20                 | 16                 | 7                     | 43 (41.3 %)                | 39.9 ± 0.1                 |
|                | 18            | 0                  | 2                  | 2                     | 4 (3.8 %)                  | 0.5 ± 0.3                  |
|                | 26            | 0                  | 0                  | 1                     | 1 (1.0 %)                  | 0                          |
|                | 31            | 0                  | 5                  | 3                     | 8 (7.7 %)                  | 1 ± 0.2                    |
|                | 33            | 4                  | 5                  | 3                     | 12 (11.5 %)                | 8.0 ± 0.4                  |
|                | 35            | 0                  | 0                  | 1                     | 1 (1.0 %)                  | 0                          |
|                | 39            | 0                  | 1                  | 1                     | 2 (1.9 %)                  | 0                          |
|                | 52            | 4                  | 8                  | 5                     | 17 (16.3 %)                | 7.0 ± 0.4                  |
|                | 58            | 2                  | 1                  | 1                     | 4 (3.8 %)                  | 3.1 ± 0.5                  |
|                | 59            | 0                  | 1                  | 0                     | 1 (1.0 %)                  | 0.5                        |
| Low risk       | 73            | 0                  | 2                  | 0                     | 2 (1.9 %)                  | 1                          |
|                | 44            | 0                  | 2                  | 3                     | 5 (4.8 %)                  | 1 ± 0.2                    |
|                | 70            | 1                  | 0                  | 0                     | 1 (1.0 %)                  | 1                          |
| Not-classified | 69/71         | 0                  | 1                  | 1                     | 2 (1.9 %)                  | 0                          |
|                | 74            | 0                  | 0                  | 1                     | 1 (1.0 %)                  | 0                          |

HPV : human papillomavirus.  
SD: standard deviation.



**Fig. 2.** Distribution of HPV types according to the histological diagnostic of the cervical biopsies, La Réunion Island, 2008–2012.

ADK = adenocarcinoma, SCC = squamous cell carcinoma, CIN = cervical intra epithelial neoplasia.

multitype infections; two thirds of which (22/32) were double infections and one third (10/32) were multiple ( $\geq 3$  or more) infections (Table 2).

Most frequent HPV types detected were 16HR (41.3 %), 52HR (16.3 %) and 33HR (11.5 %). HPV contribution differed slightly, with firstly 16HR (39.9 %), followed by 33HR (8.0 %) and 52HR (7.0 %). Only one sample did not contain DNA of HR-HPV (HPV 70LR).

Of the 63 positive biopsies, 61 (96.8 %) contained at least one HPV genotype that is contained in the 9-valent HPV vaccine. Incremental preventable fraction of HPV infections that could have been added by the new 9-valent vaccine to the current bivalent vaccine was estimated at 26.2 % (16 cases of infections by HPV 31, 33, 45, 52, 58, out of 61 cases).

Histologic diagnosis of most of the biopsies was squamous cell carcinoma (Fig. 2). HPV genotyping was not possible for 31 patients, of whom 16 were diagnosed with CIN2–3, four in situ squamous cell carcinomas, nine squamous cell carcinomas (SCC) and two in situ adenocarcinomas (ADK).

## Discussion

In this cross-sectional study, we aimed to estimate distribution and contribution of high risk and low risk HPV genotypes among ASCUS Pap smears and cervical biopsies of high-grade lesions and

cervical cancers in RUN. We highlighted the high prevalence and contribution of HPV 16, 31, 33, 51 and 52 in cervical dysplasia, precancerous lesions and cervical cancers. Importantly, we observed a large proportion of multitype infections (60 % in PAP smears, 50 % in biopsies).

We were unable to retrieve the colposcopy and biopsy results of HPV-positive ASCUS pap smears and therefore cannot estimate the number of cervical lesion. We have robust data on HPV genotyping for all ASCUS Pap smears, and performed analyses to estimate actual distribution of HPV in the population, rather than to evaluate its contribution. Nonetheless, in our cases, distribution and contribution were overlapping.

Previous studies have shown that in India, HPV 16, 18, 31 and 51 are the most prevalent genotypes [9,10] whereas in China, HPV types most frequently associated with cervical precancerous lesions are HPV 51, 52, and 58 [11,12]. Ethnic groups comprising RUN are immigrant populations that have come from Europe, Madagascar, Africa, India and China over centuries. Such migration patterns can reflect the similarity of HPV genotype distribution between RUN and Asian countries. HPV 45 genotype present in a prominent proportion of cervical neoplasia in Africa [13] was underrepresented in our population. Notably, we found a large representation of HPV 33 genotype, which is also mostly detected in high grade lesions among women in Mexico [14].

It is interesting to note that HPV51 was the most frequent HPV type in ASCUS Pap smears, whereas it was not retrieved at all in cervical biopsies. Our findings are comparable to HPV genotype distribution in cervical lesions in metropolitan France in EDITH studies [15], where prevalence of HPV51 was lower in invasive cancer and high grade lesions than in low grade lesions. This diminution is possibly related to viral clearance, with persistence of more aggressive phenotypes in more severe lesions. This may be one of the reasons why HPV51 was not eligible in the vaccine Gardasil 9.

Existing vaccines used in RUN cover HPV 16 and 18 genotypes, responsible for the majority of invasive cervical cancer in other regions. In our population, these oncogenic genotypes were found contributive in barely 40 % of positive cervical biopsies. Our data suggest the need to implement better detection and prevention strategies that reflect the geographic population. The addition of other HR HPV genotypes contained in the 9-valent vaccine (HPV 31, 33, 45, 52, 58) could increase the preventable fraction of precancerous and cancerous lesions by 26.2 %. If we account the 9-types altogether, we could increase the coverage significantly for up to 96.8 % of the cases. These results are similar to Serrano's [8]

who observed that 9-valent HPV vaccine could prevent 90 % of invasive cervical cancer cases in Brazil, Mexico, India and China (by 12–19 % with the addition of HPV 31, 33, 45, 52, 58). The HPV genotypes that are not covered by the 9-valent vaccine were considered to be low prevalence, thus vaccination could reduce the burden of cervical cancer substantially.

Nevertheless, the first step to be achieved on RUN, should be to increase vaccination coverage to directly protect children. On the island, only 8.1 % of girls aged <16 years old were fully vaccinated in 2018 (23.7 % in metropolitan France in 2018 [16]). Since December 2019, French authorities recommend gender-neutral vaccination for 11–14 years old with a nine-valent HPV vaccine [17].

Lefevre raised hypotheses to explain this low level of immunization in France based on interviews of 16 physicians [18]. First, HPV vaccine is recommended, and not mandatory, and only 65 % of the price (~120€) is reimbursed by Health Insurance for girls aged 11–19 years. The high cost burdens accessibility of the vaccines for the most disadvantaged population. Secondly, attitude of general practitioners prescribing the vaccine are mixed. Thirdly, teenage girls are little informed and invested in the decision. Parental authorization is required for children until 18 years old. Parental reluctance to HPV vaccination may be fed by conspiracy theories, suspicion of conflicts of interest and pharmaceutical lobbying. Moreover, parents often fear that vaccination may encourage their children to have early sexual intercourses, and incurs side effects, altogether leading to hesitancy.

Hitherto, there is no evidence supporting that receiving an HPV vaccine is linked to autoimmune condition, including multiple sclerosis, other demyelinating diseases, systemic lupus erythematosus, Guillain-Barré syndrome, rheumatologic disorders, type 1 diabetes, Hashimoto and Graves' diseases, and immune thrombocytopenia or haemolytic anaemia [19,20]. The increased risk of pathologies such as stroke, venous thromboembolism, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis by HPV vaccination are not supported [21].

Although vaccination policies differ between countries, countries like Australia, Canada, Denmark, United Kingdom and Italy achieve very high rates of complete vaccination coverage (70–85 %) [22–24].

Of note, Australia launched in 2007 a national publicly-funded school immunization program for HPV vaccine aiming at both sexes. Hall suggests that if high-coverage vaccination and screening is maintained, indirect effects will also affect cervical cancer incidences, with the hope of eliminating it as public health problem within the next twenty years [25]. In longer term, vaccination could also play a role on lowering prevalence of anogenital warts, through cross-protection and herd-immunity [26,27].

A limitation of our study however is the low number of samples analysed, since HPV DNA extraction was only possible in 69.1 % of biopsies. There may be multiple explanations: (a) sample quality can be impacted by handling in the operating room, formalin fixation (which may lead to fragmented nucleic acids and DNA modifications), paraffin embedding and storage methods [28]; (b) total yield of viral nucleic acid from a clinical specimen is dependent on the specimen's volume, the initial virus concentration and the effectiveness provided by the extraction method [29]. Not only cervical biopsies are minute in quantity of tissue samples, but also QIAGEN may not be the most powerful technique.

This high rate of failure to test FFPE can introduce a selection bias if positive samples were not representative of the total pool of analysed biopsies. However, age distribution and histologies found in women with non-contributive biopsies for HPV genotyping were not different from those analysed ( $p = 0.16$ ).

In addition, Hybrid Capture 2 test can only detect 13 high-risk HPV genotypes. Moreover, only samples containing more than 200 000 DNA copies of viral genome (>2 pg/mL) were analysed for HPV genotyping. INNO-LIPA test also has lower sensitivity than other methods such as real time PCR, therefore this test cannot recognize all genotypes. In addition, primer that targets L1 region of HPV genome may give rise to inaccuracies as target sequence can be fragmented or deleted when viral genome is integrated into cell genome. Some of the problems associated with reduced sensitivity can underestimate the overall prevalence of HPV DNAs in our population.

To improve the description of distribution of HPV genotypes in the future, investment into modern and more performing devices should be made and improvements of the conditions of samples' storage are needed.

## Conclusion

We reported the high prevalence and contribution of HPV 16, 31, 33, 51 and 52 genotypes in cervical dysplasia, precancerous lesions and cervical cancer on RUN. As these genotypes are included in the 9-valent vaccine, immunization with this vaccine should be effective, and in the long term, have a positive impact on reduction of cervical cancer incidence. Before implementing this strategy on the island, immunization uptake has to be improved. This study should support a proposal to introduce vaccination in middle schools, for both girls and boys, and to foster information about HPV vaccination among parents and general practitioners.

## Details of ethics approval

This study was approved by the local ethical committee and the National Commission for Informatics and Liberty, the French Data Protection Authority. All participants provided their informed consent for this study.

## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Supported by grants from the *Appel d'offre interne de la recherche médicale du CHU de La Réunion 2012*. The funding body allowed us to buy material for HPV genotyping. It did not have any role, neither in the design of the study, nor in the collection, analysis and interpretation of data, nor in writing the manuscript.

## Contribution to authorship

The authors meet all the criteria set out in the journal's authorship criteria. Most particularly, AM, CF, PA, MB and PG conceptualized and designed the study. NZ, PLT, NAY and AB participated in the acquisition, analysis and interpretation of data. PLT and AB drafted the initial manuscript. PG, MB, NAY and CF critically reviewed the manuscript. All authors read and approved the final manuscript.

## Declaration of Competing Interest

The authors declare that there are no conflicts of interest.



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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2020.07.001>.

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## **Article 2.** Freins à la vaccination contre le papillomavirus à La Réunion

### Résumé

Introduction : A l'île de La Réunion (RUN), le cancer du col de l'utérus est le 4ème cancer le plus fréquent chez la femme et le taux de mortalité standardisé est de 4,8 pour 100 000 femmes. Il est évitable par la vaccination contre le papillomavirus (HPV), mais seulement 8,1% des jeunes filles âgées de moins de 16 ans sont complètement vaccinées.

Objectif : Déterminer les facteurs liés à l'hésitation de la vaccination HPV à La Réunion.

Méthodes : Entre janvier et juin 2017, les médecins généralistes, sages-femmes et gynécologues libéraux ont été invités par mail à répondre à un auto-questionnaire en ligne. Des questionnaires ont également été distribués aux mamans ayant des filles âgées de 11 à 19 ans, dans 2 collèges du Sud de La Réunion. Les données ont été recueillies à l'aide de Google Form.

Résultats : Au total, 125 professionnels de santé et 85 mères ont répondu au questionnaire. Les connaissances sur l'infection par les HPV étaient insuffisantes. Toutes les personnes interrogées ont exprimé des inquiétudes concernant la vaccination contre le HPV, en raison des réactions auto-immunes, et du manque d'efficacité. Les mères se sentaient insuffisamment encouragées par leurs médecins généralistes à vacciner leurs enfants.

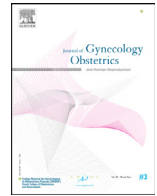
Conclusions : A La Réunion, le manque d'information et la méfiance vis-à-vis de la vaccination de la part des parents mais aussi des soignants, sont les principaux facteurs contribuant à la faible couverture vaccinale contre le HPV. Des formations destinées aux soignants et des campagnes d'information de la population générale pourraient jouer un rôle dans l'augmentation de la couverture vaccinale ; l'école pourrait sensibiliser les adolescents.



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Original Article

## HPV vaccination hesitancy in Reunion Island

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### ABSTRACT

**Introduction:** In Reunion Island (RUN), cervical cancer is the 4th most common cancer in women and standardized mortality rate is 4.8 for 100 000 women. It is preventable by HPV vaccination, yet only 8.1% of girls aged <16 years old are fully vaccinated.

**Objective:** To determine factors related to HPV vaccination hesitancy in Reunion Island.

**Study Design:** Between January and June 2017, general practitioners, midwives and liberal gynaecologists were invited by email to answer an online self-questionnaire. Questionnaires were also distributed to mothers who had daughters aged between 11 and 19 years old, in 2 middle schools in Southern Reunion. Data was collected using Google Form.

**Results:** 125 health professionals and 85 mothers answered the questionnaire. Knowledge about HPV infection was not sufficient. All people interviewed expressed concerns about HPV vaccination, because of autoimmune reactions, and lack of efficacy. Mothers felt insufficiently encouraged by their general practitioners to vaccinate their children.

**Conclusions:** In Reunion Island, lack of information and vaccination mistrust from parents as well as from caregivers, are the main factors contributing to low HPV vaccination coverage. Formations intended for caregivers and information campaigns of general population could play a role into raising vaccination coverage; school could enhance teenagers' awareness.

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### Introduction

Cervical cancer is the second most frequent solid neoplasm in woman [1], and the fourth leading cause of cancer-related mortality worldwide [2]. Cervical cancer is commonly associated with a persistent Human Papillomavirus (HPV) infection, which induces cervical cell abnormalities that progress towards cervical carcinogenesis.

In Reunion Island (RUN), a French territory located in the Indian Ocean near Madagascar, the standardized incidence and mortality rate in 2012 were twice higher than in Metropolitan France (10.8 and

4.8 for 100 000 women respectively) [3,4], yet vaccination coverage is insufficient.

Higher incidence of cervical cancer can be explained by low screening coverage but also by a population in RUN with more risk factors (high parity, early sexual activity) [5] and more HPV coinfections [6].

Despite French authorities recommending gender-neutral vaccination for 11–14 years old with a nine-valent HPV vaccine [7] since December 2019, only 8.1% of girls aged <16 years old in RUN were fully vaccinated in 2018 (23.7% in metropolitan France in 2018 [8]).

In this study, we aimed to determine factors related to HPV vaccination hesitancy in Reunion Island in view of potentially improving vaccination coverage in the at-risk population.

### Material and methods

We carried out a descriptive, observational, departmental study, between January and June 2017.

**Abbreviations:** GP, general practitioners; HP, health professionals; HPV, human papillomavirus; LG, liberal gynaecologists; MW, midwives; RUN, Reunion Island

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## Evaluation of health professionals (HP)

General practitioners (GP), midwives (MW) and liberal gynaecologists (LG) affiliated to the Repere (perinatal network of Reunion Island) were invited by email to answer an online self-questionnaire, (Appendix A). A second round of invitations was sent a few months later.

Knowledge about HPV vaccination was evaluated through 11 questions. The rest of the questionnaire was designed in multiple-choice format to standardize opinions surrounding the same theme. Opportunities for free text comments were also available. Participation was voluntary, unpaid and anonymous.

Data was collected using Google Form and statistical analysis performed by Google Sheet. Qualitative variables were expressed as numbers and percentages, and quantitative variables as means  $\pm$  standard deviation.

## Evaluation of mothers

Questionnaires (Appendix B) were distributed to mothers who had daughters aged between 11 and 19 years old, in 2 middle schools in Saint Pierre (South RUN). A total of 320 questionnaires were distributed: 200 in one of the schools, and 120 in the other. Teachers diffused the questionnaire to girls in 8th and 9th grade.

## Results

A flowchart of the study is exposed in Fig. 1.

### Evaluation of health professionals

A total of 125 HP responses were obtained: 77 GP, 36 MW, 10 LG and 2 who did not specify their occupation.

#### Knowledge – question 2 to 12 (Table 1)

Knowledge about HPV was poor with the majority. The responders underestimated risks related to HPV infection (30%), conization (41%), cervical cancer severity (78%) or vaccination efficiency (32%). Nonetheless, recommendations for HPV vaccination and Pap smear were well-known (83% and 74% respectively). GPs were particularly sensitized to the possibilities of co-administration of HPV vaccines, unlike MW (87% VS 39%), who scarcely prescribe other vaccines.

#### Table 1

#### Vaccination (Table 2 and Appendix C)

Among participants, 31% routinely recommended the HPV vaccine for their patients (mostly LG 60%) while 28% never or scarcely offered it.

#### Table 2

Scores for Question 2 to 7 were established for GP and LG, according to exactitude of answers: 35 obtained a high score (score between 4 and 6 good answers) and 52 a weak score (<2).

Among those with a high score, 57% declared that they systematically offered HPV vaccination, none of them indicated never to have offered vaccination. Conversely, among those that achieved a poor score, 38% never or rarely offered HPV vaccination.

#### Vaccination hesitancy

Most participants had a favorable attitude towards vaccination in general (92%), though much less so towards HPV vaccination specifically (71%); MW specifically were the most hesitant (56%). GPs who expressed concerns about aluminum-containing vaccinal adjuvants and auto-immune reactions were less frequently to prescribe HPV vaccine.

Notwithstanding vaccine efficacy, participants (60%) believed that more hindsight experience and data concerning efficacy and safety was needed before generalizing the vaccine.

Other perceived barriers to vaccination related to attitudinal fear for diminution of Pap smear coverage (62%), high costs (52%), and belief in conflicts of interest with pharmaceutical companies (30%).

#### Vaccination acceptability

Twenty participants declared that they did not offer HPV vaccination. Most GP (66%) felt rejected or unheard by patients. Only 25% report experiences wherein they managed to convince their patients after thorough informative discussion.

#### Improvements to be made

Most participants (74%) consider themselves well-informed about HPV vaccination, though they felt more effective communication tools or flyers are necessary to initiate/improve the dialog with their patients (82%). To improve vaccination coverage, GPs suggest that vaccination should be offered through a dedicated consultation (61%), citing time constraints during routine consultations as a barrier. Additionally, 67% agreed that efforts to lower age of vaccination should also be considered; co administrating HPV vaccine with Tdap-IPV (tetanus, diphtheria, pertussis, polio) vaccine for example may raise vaccination coverage.

### Evaluation of mothers

Among 320 distributed questionnaires in schools, 85 were retrieved for analysis. Ten mothers had a personal history of conization of cervical laser, though among them, 60% declared no previous history of HPV infection (Appendix D).

Mothers were more favorable to general vaccination (73%), than to HPV vaccination, with 40% of mothers unfavorable (rather not favorable/ not favorable), because they feared side effects of vaccination (65%) (Appendix E).

A minority (18%) however did vaccinate or expressed intent to vaccinate their daughter following a parent-child discussion (72%).

Mothers were asked four questions concerning their knowledge about HPV; higher scores indicated awareness of HPV vaccine benefits. Analysis returned a mean score of 1.5/4, indicating a broad lack of perceived benefit.

Mothers cited their main source of information to be from GP or gynecologists (49%), whereas others were getting information from media, internet, and friends. Given that 94% of mothers reported fully entrusting advice from their GP; a professional recommendation was therefore a key factor in their decision-making. Notably, 31% of mothers reported not having received any recommendation to vaccinate from GP.

## Discussion

Knowledge about HPV infection among caregivers was not sufficient. They underestimated the risk of being infected, the burden of cervical cancer and associated mortality rate, or the efficiency of HPV vaccine. On the other hand, they over estimated Pap smear sensitivity. As such, some professionals claimed that vaccinated patients may worsen the compliance into cervical cancer screening, and this could raise CC incidence.

Our study highlighted multiple factors that may contribute to HPV vaccinal hesitancy. Many will have concerns for adverse effects such as the induction of an auto-immune reaction; yet since licensure of HPV vaccines, Global Advisory Committee on Vaccine Safety has found no adverse events of concern based on many very large, high quality studies over several million persons [9]. In her meta-analysis, Mouchet found no association between HPV vaccine and risk of demyelinating diseases [10].

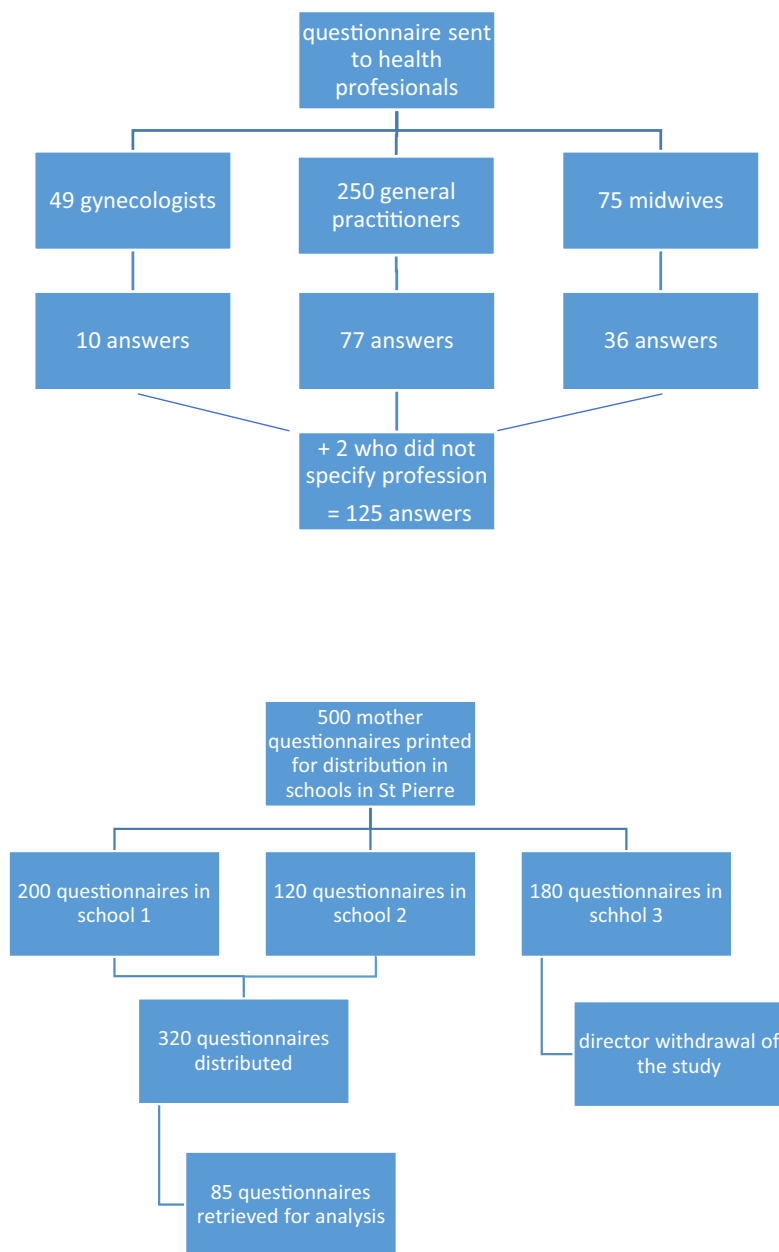


Fig. 1. Flow charts for questionnaires distribution.

Table 1 Knowledge among health professionals.

| Question  | Correct answer expected     | Proportion of good answer |                     |                     |                     |
|---|-----------------------------|---------------------------|---------------------|---------------------|---------------------|
|   |                             | Total, n = 124<br>n (%)   | GP, n = 77<br>n (%) | MW, n = 36<br>n (%) | LG, n = 10<br>n (%) |
| 2. What is the probability for a woman during her life to get infected by HPV?                                      | 80%                         | 51 (41%)                  | 39 (51%)            | 8 (22%)             | 4 (40%)             |
| 3. What is the proportion of cervical cancers imputable to HPV 16–18?   | 70%                         | 80 (64%)                  | 46 (60%)            | 25 (69%)            | 8 (80%)             |
| 4. Among vaccinated patients, what is HPV vaccine efficiency? (measured by the rate of reinfection by targeted HPV) | 100%                        | 50 (40%)                  | 33 (43%)            | 13 (36%)            | 4 (40%)             |
| 5. What is the expected reduction of cervical cancer among vaccinated women?  | 70-100%                     | 57 (46%)                  | 34 (44%)            | 15 (42%)            | 7 (70%)             |
| 6. What is the mortality rate in case of cervical cancer?   | 60%                         | 24 (19%)                  | 13 (17%)            | 7 (25%)             | 4 (40%)             |
| 7. Do you think that conizations could cause obstetrical conditions?  | Yes most probably           | 43 (35%)                  | 26 (34%)            | 14 (39%)            | 3 (30%)             |
| 8. Which obstetrical complication is possible because of conization?  | premature delivery          | 65 (52%)                  | 38 (49%)            | 17 (47%)            | 9 (90%)             |
| 9. According to French recomandations, when should HPV vaccination be realized?                                     | 11-14 years                 | 104 (83%)                 | 69 (90%)            | 26 (72%)            | 8 (80%)             |
| 10. Do you think that HPV vaccine can be co administrated with other vaccines?                                      | yes                         | 82 (66%)                  | 67 (87%)            | 11 (39%)            | 4 (40%)             |
| 11. When should Pap smear be performed?   | every 3 years from 25 years | 92 (74%)                  | 56 (73%)            | 28 (78%)            | 7 (70%)             |
| 12. Among patients with cervical cancer, what is the rate of patients with a normal recent (<3 years) Pap smear?    | 20-30%                      | 25 (20%)                  | 15 (19%)            | 7 (19%)             | 2 (20%)             |

**Table 2**  
Evaluation of health professionals.

| Question   |                                       | Total, n = 124<br>n (%) |
|--|---------------------------------------|-------------------------|
| 13. Are you favorable to vaccination in general?   | Yes - rather yes                      | 114 (92)                |
| 14. Are you favorable to HPV vaccination?  | Yes                                   | 78 (71)                 |
| 15. Do you feel confident when prescribing vaccination?  | Confident                             | 89 (71)                 |
| 16. Do you feel confident when prescribing HPV vaccination?  | Confident                             | 59 (47)                 |
| 17. Do adjuvants such as aluminum in vaccines, represent a risk to you?  | Yes maybe but benefit is superior     | 58 (46)                 |
| 18. Do controversies surrounding HPV vaccine, including risk of auto immune diseases or multiple sclerosis, limit your prescription (without taking into account patient's opinion)? | Yes partly                            | 34 (27)                 |
| 19. Would you think that more evidence of long-term efficacy concerning HPV vaccine is needed to generalize its prescription?  | Yes you totally agree /rather agree   | 75 (60)                 |
| 20. Do you think that pharmaceutical laboratories may have had an impact on vaccinal recommendations in France?  | Yes you totally agree                 | 47 (38)                 |
| 21. Do you think that conflict of interests between pharmaceutical laboratories and French authorities, induced concealment of vaccines side-back effects?                           | Yes you totally agree                 | 37 (30)                 |
| 22. Do you think that HPV vaccine is too expensive, especially since Pap smear screening is still necessary?   | Yes you totally agree / rather yes    | 65 (52)                 |
| 23. Do you think that vaccinated patients may be less observant concerning Pap smear screening?  | Yes a majority / minority of patients | 78 (62)                 |
| 24. Do you think that HPV referring to sexual activity, may limit the prescription or acceptance of HPV vaccination?   | You don't agree                       | 55 (44)                 |
| 25. Do you think that adjuvants such as aluminum in vaccines, may participate in hesitancy towards patients and/or their parents in Reunion Island?                                  | Probably for some                     | 69 (55)                 |
| 26. Do you think that controversies surrounding vaccination in general, including hepatitis B, may participate to HPV vaccination refusal among patients and/or their family?        | Sometimes                             | 47 (38)                 |
| 27. Do you think that controversies surrounding HPV vaccination, may be a cause of refusal for HPV vaccination?  | Often                                 | 43 (44)                 |
| 28. Do you recommend HPV vaccine?  | Systematically >90%                   | 39 (31)                 |
|  | Never                                 | 20 (16)                 |
| 29. When you offer vaccination in general, how often do patients refuse?   | Rarely                                | 64 (88)                 |
| 30. When you offer HPV vaccination, how often do patients refuse?  | Often                                 | 35 (31)                 |
|  | Rarely                                | 38 (33)                 |
| 31. After explaining benefits and risk, do you manage to change patients' mind towards HPV vaccination?  | Frequently/ Often                     | 31 (25)                 |
| 32. Do you think that patients more prone to alternative medicine, are more hesitant towards vaccination?  | Yes totally                           | 58 (46)                 |
| 33. Do you think that you are well-informed concerning HPV vaccination, its benefits, risks and recommendations?   | Yes totally/ Rather yes               | 92 (74)                 |
| 34. Would you be interested in communication and information tools for your patients?  | Yes / Why not                         | 103 (82)                |
| 35. Do you think that lack of time during consultations participates to low HPV vaccination coverage?  | You rather agree                      | 45 (36)                 |
| 36. Do you think that a dedicated consultation could improve vaccination coverage?   | Yes totally/rather yes                | 76 (61)                 |
| 37. Do you think that combining HPV vaccination with Tdap-IPV (tetanus, diphtheria, pertussis, polio) vaccine, could raise vaccination coverage?                                     | Yes totally / yes probably            | 84 (67)                 |

Another reluctance was related to vaccination efficiency, and whether the vaccine protects from all cancer-causing HPV strains. In recent studies and meta-analyses, it was proved that compared to unvaccinated women, women who benefited from HPV vaccine had a reduced risk of HPV infection, genital wart, and precancerous cervical lesions [11], and even of cervical cancer [12,13]. Hall estimated that in Australia, following actual trends with 83% HPV vaccination coverage, the annual incidence of cervical cancer could decrease and remain at fewer than one case per 100 000 women by 2066 [13]. Despite compelling evidence of HPV vaccine effectiveness and safety, limited awareness of such continues to hinder vaccine uptake.

Further, in 2017, the Regional Union of Liberal Doctors in Reunion Island (URMLR - Union régionale des Médecins Libéraux de la Réunion) published an information note questioning HPV vaccine long-term efficacy, side effects and presenting Pap smear screening as a way to cure cervical cancer. The particular weight of the anti-vaccine leagues in Reunion Island, led by Dr Philippe de Chazournes, casted a negative halo around the subject [14,15]. From our study, knowing that 94% of mothers are influenced by their GP professional opinions, often taking their advice, recommendations for these types of official publications should be reviewed more critically. Well-informed practitioners are more likely to offer HPV vaccines to their patients, as such, accuracy of communicated facts regarding will be key to overcoming this type of barrier.

In spite of hesitant caregivers, others were favorable to HPV vaccination, though they would like to have communication tools about HPV vaccination to deliver to their patients or their parents. In fact, such tools exist and are freely accessible or can be ordered [16]. Simple tools such as informational pamphlet will combat misinformation and allow patients or parents to make fully informed decisions.

Nonetheless, in Reunion Island with 22.6% of illiteracy, and its mixed population, sometimes not speaking French, other specific tools need to be implemented. To overcome language barrier, pamphlets could be translated into different languages, or they could be illustrated with easy-to-understand drawings. Indeed, it was proved that the effectiveness of vaccine communication relied on messaging in the form of storytelling with the use of gists, emotive anecdotes, and imagery [17].

Association between low education and low household income and vaccine hesitancy remains unclear, though culture and religion may influence risk perceptions. Reunion Island is particularly concerned by this mixed culture with civilizations coming from Africa/Madagascar, China, India, and Europe. A previous study showed that within migrant African population, HPV vaccine was generally unacceptable, with a mistrust from the west, from which the vaccine originates [18]. The most suspicious parents even believed HPV vaccine was a racist bio-political strategy designed to sterilize Black/African girls for population control purposes [19]. Immigrated Asian women perceived HPV vaccine would be more appropriate form promiscuous women [20], and Muslims believed HPV vaccine was incompatible with their faith which precludes premarital sex [21]

In our cohort of mothers, misinformation was reflected by the fact that 60% of mothers with a personal history of conization of cervical laser declared no previous history of HPV infection. As such, there is a proportion of mothers that were insufficiently informed by their doctor; this reflects inadequate knowledge of the association between HPV infection and their pathology.

Moreover, this misinformation may create mothers' concerns, echoing health professionals' worry. This can explain why 40% of mothers were unfavorable to HPV vaccine with 65% fearing its side

effects. These rates are comparable to those of mainland France, finding a quarter of the population unfavorable to vaccines in general, with more than 60% considering the vaccines as not effective or not safe [22].

Mediatic health crises have undermined confidence in drug industry, health authorities and medical professions. This confidence crisis should be addressed by increased communication strategies to reinstate trust and stop preconceived ideas. Key communication interventions include: information and education, reminding or recalling, enhancing community ownership, teaching skills, providing support, facilitating decision making and enabling communication [17].

Even though few mothers intended to take into account their daughter's opinion about vaccination, children should be informed about their right to benefit from HPV vaccination as well. School could be the ideal place for sexual education and HPV vaccine awareness.

Another brake to vaccination was its high cost: about 130€ per dose, and two to three doses are necessary according to age. This argument is now obsolete in France since a decree was published in November 2020 registering HPV vaccine among pharmaceutical specialties reimbursable to social security holders [23].

The main limitation in this study was selection bias. Health professionals who answered the questionnaire were not representative of the caregivers in Reunion Island. Only few mothers agreed to participate. It is possible that due to the high rate of illiteracy in the population, some were not able to understand the questionnaire. Moreover, questionnaire was distributed in 2017, at the time when HPV vaccination was recommended to girls only.

## Conclusion

In Reunion Island, lack of information and vaccination mistrust from parents as well as from GP, are the main factors contributing to low HPV vaccination coverage. Formations intended for caregivers could play a role into raising vaccination coverage; filling information gaps with more facts is needed. It could promote their adherence to HPV vaccination and thus, promote their recommendation to patients. Information campaigns of general population (through communication tools such as flyers) should be reinforced, and school could enhance teenagers' awareness.

## Ethics in publishing

This research does not meet the definition of research involving the human person. According to French law (article R1121–1, decree n°2017–884 of 9 May 2018 - art.2), it does not require any CPP or ethics committee. According to GDPR (General Data Protection Regulation) in our university hospital center, all participants were informed that, in the absence of their disagreement, the data collected during this unpaid, voluntary, and anonymous questionnaire, may be used for research purposes.

## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Author contributions

The authors meet all the criteria set out in the journal's authorship criteria.

**Tran:** conceptualization, writing original draft; **Bruneteaux:** Conceptualization, methodology, software, investigation; **Lazaro:** review and editing; **Bertolotti:** writing – review and editing; **Boukerrou:** Methodology, supervision, validation

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## Appendix A. Questionnaire to health professionals

### HPV vaccination hesitancy in Reunion Island

Cervical cancer is the first cancer recognized by the World Health Organization as being related in 100% of cases to human papillomavirus (HPV) infection. It affects 3000 women in France every year and is responsible for 1000 deaths.

In addition, HPV infections are responsible for cervical lesions requiring follow-up which can be long and distressing for patients. Surgical treatments can have obstetrical consequences, sometimes severe, in women who are frequently of childbearing age. HPV is also responsible for other cancers, such as vulva, vagina, anus and oropharyngeal cancers.

Finally, HPV vaccination (Gardasil) also offers protection against genital warts, which can have a significant psychological impact and whose recurrence can make treatment difficult. Primary prevention of cervical lesions is possible through vaccination targeting papillomaviruses (HPV vaccination). This is offered in France since 2007. Nevertheless, vaccination coverage remains below 20%.

This questionnaire is anonymous. The purpose of this study is to gather the opinion of general practitioners, liberal gynecologists and midwives about HPV vaccine and about factors that may explain poor vaccination coverage, particularly in Reunion Island. Thank you in advance for your participation.

- Are you
  - general practitioner
  - midwife
  - gynecologist
2. What is the probability for a woman during her life to get infected by HPV?
  - 20%
  - 50%
  - 80%
  - 100%
  - You don't know
3. What is the proportion of cervical cancers imputable to HPV 16-18?
  - 100% of uterus cervical cancer
  - 70% of uterus cervical cancer
  - 50% of uterus cervical cancer
  - You don't know
4. Among vaccinated patients, what is HPV vaccine efficiency? (measured by the rate of reinfestation by targeted HPV)
  - 20%
  - 50%
  - 70%

- 100%
- You don't know
- 5. What is the expected reduction of cervical cancer among vaccinated women?
  - 20%
  - 50%
  - 70%
  - 100%
  - You don't know
- 6. What is the mortality rate in case of cervical cancer?
  - 90%
  - 60%
  - 30%
  - 10%
  - You don't know
- 7. Do you think that conizations could cause obstetrical conditions?
  - Yes surely
  - Yes probably
  - Yes but scarcely
  - No
- 8. Which obstetrical complication is possible because of conization?
  - Preeclampsia
  - Premature rupture of membranes and premature delivery
  - Early miscarriage
  - You don't know
- 9. According to French recommendations, when should HPV vaccination be realized?
  - 18 years old
  - During the 1st year following 1st sexual intercourse
  - 14 years old, with catch up between 15 ans 23
  - Between 11 and 14, and catch up between 15 ans 19
  - You don't know
- 10. Do you think that HPV vaccine can be co administrated with Tdap-IPV (tetanus, diphteria, pertussis, polio) vaccine?
  - Yes
  - No
  - You don't know
- 11. When should Pap smear be performed?
  - Every year between 18 and 65 years old
  - Every 3 years between 18 and 65 years old after 2 normal yearly Pap smear
  - Every year between 25 and 65 years old
  - Every 3 years between 25 and 65 years old after 2 normal yearly Pap smear
  - You don't know
- 12. Among patients with cervical cancer, what is the rate of patients with a normal recent (<3 years) Pap smear?
  - None or exceptional
  - 2-3%
  - 20-30%
  - You don't know
- 13. Are you favorable to vaccination in general?
  - Yes
  - Rather yes
  - Rather no
  - No
- 14. Are you favorable to HPV vaccination?
  - Yes
  - Rather yes
  - Rather no
  - No
- 15. Do you feel confident when prescribing vaccination?
  - Confident
  - Mildly confident
  - Not very confident
  - Not confident
- 16. Do you feel confident when prescribing HPV vaccination?
  - Confident
  - Mildly confident
  - Not very confident
  - Not confident
- 17. Do adjuvants such as aluminum in vaccines, represent a risk to you?
  - Yes
  - Yes maybe but benefit is superior
  - Yes maybe thus you limit your prescriptions to compulsory vaccines only
  - Maybe but you are not worried
  - No, safety was proved
  - Other : .....
- 18. Do controversies surrounding HPV vaccine, including risk of autoimmune diseases or multiple sclerosis, limit your prescription (without taking into account patient's opinion)?
  - Yes
  - Yes partly
  - No, benefit of vaccination is superior
  - No, you think there is no statistical evidence
  - You agree with the last 2 propositions above
  - Others : .....
- 19. Would you think that more evidence of long-term efficacy concerning HPV vaccine is needed to generalize its prescription?
  - Yes you totally agree
  - You rather agree
  - You don't quite agree
  - You don't agree
  - Other : .....
- 20. Do you think that pharmaceutical laboratories may have had an impact on vaccinal recommendations in France?
  - Yes you totally agree
  - Rather yes
  - Rather no
  - No
- 21. Do you think that conflict of interests between pharmaceutical laboratories and French authorities, induced concealment of vaccines side-back effects?
  - Yes totally
  - Yes sometimes
  - Yes in some cases
  - No
  - You don't know
- 22. Do you think that HPV vaccine is too expensive, especially since Pap smear screening is still necessary?
  - Yes you totally agree
  - Rather yes
  - Rather no
  - No
- 23. Do you think that vaccinated patients may be less observant concerning Pap smear screening?
  - Yes, a majority of patients
  - Yes, a minority of patients
  - Rarely
  - No
- 24. Do you think that HPV referring to sexual activity, may limit the prescription or acceptation of HPV vaccination?
  - Yes you totally agree
  - You quite agree
  - You don't agree
  - You don't know
- 25. Do you think that adjuvants such as aluminum in vaccines, may participate in hesitancy towards patients and/or their parents in Reunion Island?
  - Totally

- Probably for some
  - For a minority
  - No
  - You don't know
26. Do you think that controversies surrounding vaccination in general, including hepatitis B, may participate to HPV vaccination refusal among patients and/or their family?
- Yes, very frequently
  - Often
  - Sometimes
  - Rarely
  - Never
27. Do you think that controversies surrounding HPV vaccination, may be a cause of refusal for HPV vaccination?
- Frequently
  - Often
  - Sometimes
  - Rarely
  - Never
28. Do you recommend HPV vaccine?
- Systematically of >90%
  - In 50-90% of targeted population
  - 10-50% of targeted population
  - Rarely <10%
  - Never
29. When you offer vaccination in general, how often do patients refuse?
- Frequently
  - Often
  - 50% of cases
  - Rarely
  - Not concerned
30. When you offer HPV vaccination, how often do patients refuse?
- Frequently
  - Often
  - 50% of cases
  - Rarely
31. After explaining benefits and risk, do you manage to change patients' mind towards HPV vaccination?
- Frequently
  - Often
  - Sometimes
  - Rarely
  - Never
  - You don't know
32. Do you think that patients more prone to alternative medicine, are more hesitant towards vaccination?
- Yes totally
  - Rather yes
  - Rather no
  - No
  - You don't know
33. Do you think that you are well-informed concerning HPV vaccination, its benefits, risks and recommendations?
- Yes, totally
  - Rather yes
  - Rather no
  - No
34. Would you be interested in communication and information tools for your patients?
- Yes
  - Why not
  - No
35. Do you think that lack of time during consultations participates to low HPV vaccination coverage?
- You totally agree

- You rather agree
  - You don't agree
  - You don't know
36. Do you think that a dedicated consultation could improve vaccination coverage?
- Yes totally
  - Rather yes
  - Rather no
  - No
  - You don't know
37. Do you think that combining HPV vaccination with Tdap-IPV (tetanus, diphtheria, pertussis, polio) vaccine, could raise vaccination coverage?
- Yes, totally
  - Yes probably
  - No
  - You don't know

**Appendix B. Questionnaire to mothers about HPV (Human Papillomavirus) vaccination**

How old are you?

.....

How old is/are your daughter(s)?

.....

What is your educational level?

- middle school
- high school
- university

What is your profession?

- Unemployed
- Employee
- Senior executive
- Medical/paramedical

Have you ever been concerned by:

- HPV infection
- yes  no
- 
- Cervical pathology related to HPV which needed follow-up
- yes  no
- 
- Benign cervical pathology which needed treatment by laser and/or conization
- yes  no
- 
- Cervical cancer
- yes  no

Do you know somebody, in your family or friends, who was concerned by:

- HPV infection
- yes  no

- Cervical pathology related to HPV which needed follow-up

yes  no

- Benign cervical pathology which needed treatment by laser and/or conization

yes  no

- Cervical cancer

yes  no

According to you, HPV is responsible for:

- 100% of uterine cervical cancer
- 80% of uterine cervical cancer
- 50% of uterine cervical cancer
- 30% of uterine cervical cancer
- 10% of uterine cervical cancer
- You don't know

About HPV transmission, do you think that:

- HPV can be transmitted during sexual intercourse

true  false  you don't know

- HPV can be transmitted only in case of multiple partners

true  false  you don't know

- Condoms safely prevents transmission

true  false  you don't know

What is your opinion concerning HPV vaccination:

- totally favorable
- rather favorable
- rather not favorable
- not favorable
- no opinion

Are your daughter(s)/ Will your daughter(s) be vaccinated against HPV?

Yes  
 No  
 you don't know

Do you/ are you going to gather their opinion before vaccinating them against HPV?

Yes, and you will respect it  
 Yes but you will make the final decision  
 No  
 You don't know

About vaccination in general, are you:

- totally favorable
- rather favorable
- rather not favorable
- not favorable
- no opinion
- it depends on which vaccine. Can you precise your opinion?  
.....

Do you think that HPV vaccination is useful?

Yes  
 No. Why? .....  
 No opinion

Do you think that it could induce severe side-back effects?

Totally agree  
 Rather agree  
 Rather don't agree  
 Don't agree  
 No opinion

Do you want to bring some precisions? .....

Do you fearvaccinaladjuvants?

Yes, thus you refuse vaccination  
 Yes but without calling into question vaccination  
 No  
 No opinion

What does your knowledge about HPV rely on?

- Media (TV, radio)
- Internet general websites
- Official governmental websites
- Forum, blog
- Friends, family
- General practitioner or gynecologist
- Other. Please precise: .....

To what extent could the advice given by your general practitioner or gynecologist about HPV vaccination influence your decision?

You follow his/her advice  
 You take the advice into account but you look for more information (friends, family, media, internet)  
 You don't follow the advice. Why? .....

Has your general practitioner talked to you about HPV vaccination for your daughter?

Yes, he/she offered it  
 Yes, he/she talked about it without really offering it  
 Yes, but he/ she did not recommend it  
 No

Do you have comments?

.....  
Thank you for your participation

**Appendix C. Detailed answers to health professionals questionnaires**

| Question  | Total, n=124 n (%) | GP, n = 77 n (%) | LG, n = 10 % | MW, n = 36 n (%) |
|---|--------------------|------------------|--------------|------------------|
| 13. Are you favourable to vaccination in general?   | 77 (62)            |                  |              | 14 (39)          |
| Yes   | 37 (30)            |                  |              | 17 (48)          |
| Rather yes  | 10 (8)             |                  |              |                  |
| Rather no - No  |                    |                  |              |                  |
| 14. Are you favourable to HPV vaccination?  | 52 (42)            | 37 (48)          | 5 (50)       | 10 (28)          |
| Yes   | 26 (29)            | 22 (29)          | 3 (30)       | 10 (28)          |
| Rather yes  |                    |                  |              |                  |
| Rather no   |                    |                  |              |                  |
| No  |                    |                  |              |                  |
| 15. Do you feel confident when prescribing vaccination?   | 89 (71)            | 65 (84)          |              | 17 (47)          |
| Confident   | 30 (24)            | 11 (14)          |              | 14 (39)          |
| Mildly confident  | 5 (4)              | 1 (1)            |              | 4 (11)           |
| Not very confident  | 1 (1)              | 0                |              | 1 (3)            |
| 16. Do you feel confident when prescribing HPV vaccination?   | 59 (47)            | 39 (51)          |              | 13 (36)          |
| Confident   | 33 (26)            | 23 (30)          |              | 8 (22)           |
| Mildly confident  | 19 (16)            | 8 (10)           |              | 9 (25)           |
| Not very confident  |                    |                  |              |                  |
| Not confident   | 14 (11)            | 7 (9)            |              | 6 (17)           |
| 17. Do adjuvants such as aluminium in vaccines, represent a risk to you?  | 10 (8)             |                  |              |                  |
| Yes totally   | 58 (46)            |                  |              |                  |
| Yes maybe but benefit is superior   | 15 (12)            |                  |              |                  |
| Yes maybe it limits my prescription   | 20 (16)            |                  |              |                  |
| Maybe but I am not worried  | 19 (15)            |                  |              |                  |
| No, safety was proved   | 3 (2)              |                  |              |                  |
| Other   | 9 (7)              |                  |              |                  |
| 18. Do controversies surrounding HPV vaccine, including risk of autoimmune diseases or multiple sclerosis, limit your prescription (without taking into account patient's opinion)? | 34 (27)            |                  |              |                  |
| Yes   | 22 (18)            |                  |              |                  |
| Yes partly  | 22 (18)            |                  |              |                  |
| No benefit of vaccination is superior   |                    |                  |              |                  |
| No you think there is no statistical evidence   | 33 (26)            |                  |              |                  |
| You agree with the last 2 propositions above  | 5 (4)              |                  |              |                  |
| Other   | 5 (4)              |                  |              |                  |
| 19. Would you think that more evidence of long-term efficacy concerning HPV vaccine is needed to generalize its prescription?   | 38 (30)            |                  |              |                  |
| Yes you totally agree   | 37 (30)            |                  |              |                  |
| You rather agree  | 14 (11)            |                  |              |                  |
| You don't quite agree   | 31 (25)            |                  |              |                  |
| You don't agree   | 5 (4)              |                  |              |                  |
| Other   |                    |                  |              |                  |
| 20. Do you think that pharmaceutical laboratories may have had an impact on vaccinal recommendations in France?   | 47 (38)            |                  |              |                  |
| Yes you totally agree   | 56 (45)            |                  |              |                  |
| Rather yes  | 20 (16)            |                  |              |                  |
| Rather no   | 2 (1)              |                  |              |                  |
| No  |                    |                  |              |                  |
| 21. Do you think that conflict of interests between pharmaceutical laboratories and French authorities, induced concealment of vaccines side-back effects?                          | 37 (30)            |                  |              |                  |
| Yes you totally agree   | 41 (33)            |                  |              |                  |
| Yes sometimes   | 19 (15)            |                  |              |                  |
| Yes in some cases   | 18 (14)            |                  |              |                  |
| No  | 10 (8)             |                  |              |                  |
| You don't know  |                    |                  |              |                  |
| 22. Do you think that HPV vaccine   | 29 (23)            |                  |              |                  |
| Yes you totally agree   |                    |                  |              |                  |

(continued)

(Continued)

| Question  | Total, n=124 n (%) | GP, n = 77 n (%) | LG, n = 10 % | MW, n = 36 n (%) |
|---|--------------------|------------------|--------------|------------------|
| is too expensive, especially since Pap smear screening is still necessary?  | 36 (29)            |                  |              |                  |
| Rather yes  | 41 (33)            |                  |              |                  |
| Rather no   | 18 (15)            |                  |              |                  |
| 23. Do you think that vaccinated patients may be less observant concerning Pap smear screening?   | 25 (20)            |                  |              |                  |
| Yes a majority of patients  | 53 (42)            |                  |              |                  |
| Yes a minority of patients  | 19 (15)            |                  |              |                  |
| Rarely  | 28 (23)            |                  |              |                  |
| No  | 11 (8)             |                  |              |                  |
| 24. Do you think that HPV referring to sexual activity, may limit the prescription or acceptance of HPV vaccination?  | 47 (38)            |                  |              |                  |
| Yes you totally agree   | 55 (44)            |                  |              |                  |
| You quite agree   | 12 (10)            |                  |              |                  |
| You don't agree   |                    |                  |              |                  |
| You don't know  |                    |                  |              |                  |
| 25. Do you think that adjuvants such as aluminum in vaccines, may participate in hesitancy towards patients and/or their parents in Reunion Island?                           | 11 (9)             |                  |              |                  |
| Totally   | 69 (55)            |                  |              |                  |
| Probably for some   | 31 (25)            |                  |              |                  |
| For a minority  | 10 (8)             |                  |              |                  |
| No  | 4 (3)              |                  |              |                  |
| You don't know  |                    |                  |              |                  |
| 26. Do you think that controversies surrounding vaccination in general, including hepatitis B, may participate to HPV vaccination refusal among patients and/or their family? | 28 (22)            |                  |              |                  |
| Yes very frequently   | 44 (35)            |                  |              |                  |
| Often   | 47 (38)            |                  |              |                  |
| Sometimes   | 6 (5)              |                  |              |                  |
| Rarely  | 0                  |                  |              |                  |
| Never   |                    |                  |              |                  |
| 27. Do you think that controversies surrounding HPV vaccination, may be a cause of refusal for HPV vaccination?   | 38 (30)            |                  |              |                  |
| Frequently  | 43 (44)            |                  |              |                  |
| Often   | 36 (29)            |                  |              |                  |
| Sometimes   | 6 (5)              |                  |              |                  |
| Rarely  | 2 (2)              |                  |              |                  |
| Never   |                    |                  |              |                  |
| 28. Do you recommend HPV vaccine?   | 39 (31)            | 28 (36)          |              | 5 (13)           |
| Systematically >90%   | 33 (26)            | 21 (27)          |              | 9 (25)           |
| 50-90% of targeted population   | 18 (15)            | 11 (14)          |              | 4 (13)           |
| 10-50%  | 15 (12)            | 10 (13)          |              | 5 (13)           |
| <10%  | 20 (16)            | 7 (9)            |              | 16 (36)          |
| Never   | 0                  |                  |              |                  |
| 29. When you offer vaccination in general, how often do patients refuse?  | 9 (8)              |                  |              |                  |
| Frequently  | 4 (4)              |                  |              |                  |
| Often   | 64 (88)            |                  |              |                  |
| 50% of cases  |                    |                  |              |                  |
| Rarely  |                    |                  |              |                  |
| Not concerned   |                    |                  |              |                  |
| 30. When you offer HPV vaccination, how often do patients refuse?   | 13 (12)            |                  |              |                  |
| Frequently  | 35 (31)            |                  |              |                  |
| Often   | 26 (23)            |                  |              |                  |
| 50% of cases  | 38 (33)            |                  |              |                  |
| Rarely  | 31 (25)            |                  |              |                  |
| Frequently/Often  |                    |                  |              |                  |
| 31. After explaining benefits and risk, do you manage to change patients' mind towards HPV vaccination?   | 51 (41)            |                  |              |                  |
| Often   | 14 (11)            |                  |              |                  |
| Sometimes   | 29 (23)            |                  |              |                  |
| Rarely /Never   |                    |                  |              |                  |
| You don't know  |                    |                  |              |                  |
| 32. Do you think that patients more prone to alternative medicine, are more   | 58 (46)            |                  |              |                  |
| Yes totally   | 46 (37)            |                  |              |                  |
| Rather yes  | 3 (2.5)            |                  |              |                  |
| Rather no   | 3 (2.5)            |                  |              |                  |
| No  | 15 (12)            |                  |              |                  |
| You don't know  |                    |                  |              |                  |

(continued)



(Continued)

| Question   | Total, n=124 n (%)      | GP, n = 77 n (%)         | LG, n = 10 %            | MW, n = 36 n (%)       |
|--|-------------------------|--------------------------|-------------------------|------------------------|
| hesitant towards vaccination?  |                         |                          |                         |                        |
| 33. Do you think that you are well-informed concerning HPV vaccination, its benefits, risks and recommendations?                             | Yes totally 27 (22)     | Rather yes 65 (52)       | Rather no 23 (18)       | No 10 (8)              |
| Would you be interested in communication and information tools for your patients?  | Yes 56 (45)             | Why not 47 (37)          | No 22 (18)              | 35                     |
| Do you think that lack of time during consultations participates to low HPV vaccination coverage?  | You totally agree 7 (6) | You rather agree 45 (36) | You don't agree 64 (51) | You don't know 9 (7)   |
| Do you think that a dedicated consultation could improve vaccination coverage?   | Yes totally 26 (21)     | Rather yes 50 (40)       | Rather no 19 (15)       | No 14 (14)             |
| Do you think that combining HPV vaccination with Tdap-IPV (tetanus, diphtheria, pertussis, polio) vaccine, could raise vaccination coverage? | Yes totally 32 (26)     | Yes probably 52 (41)     | No 21 (17)              | You don't know 20 (16) |

**Appendix D. Mothers' characteristics**

|                                     | n = 85 |      |
|-------------------------------------|--------|------|
|                                     | n      | %    |
| ≥ 2 daughters                       | 24     | 28.2 |
| Education level                     |        |      |
| - Middle school                     | 19     | 22.3 |
| - High school                       | 23     | 27.1 |
| - University                        | 43     | 50.6 |
| Socioprofessional group             |        |      |
| - Unemployed                        | 31     | 36.5 |
| - Employee                          | 38     | 44.7 |
| - Senior executive                  | 7      | 8.2  |
| - Medical/paramedical               | 9      | 10.6 |
| Personal history related to HPV     |        |      |
| - None                              | 74     | 87   |
| - Infection                         | 5      | 5.9  |
| - Monitoring for cervical dysplasia | 4      | 4.7  |
| - Laser/conization                  | 8      | 9.4  |
| - Cervical cancer                   | 0      | 0    |
| Family history                      |        |      |
| - Infection / dysplasia             | 17     | 20   |
| - Cervical cancer                   | 12     | 14.1 |

**Appendix E. Detailed answers to mothers questionnaire**

| Question   | Total, n=85 n (%) |
|--|-------------------|
| What is your opinion concerning HPV vaccination                                    |                   |
| totally favorable  | 10 (12)           |
| rather favorable   | 20 (23)           |
| rather not favorable   | 12 (14)           |
| not favorable  | 22 (26)           |
| no opinion   | 21 (25)           |
| Are your daughter(s)/ Will your daughter(s) be vaccinated against HPV?             |                   |
| yes  | 15 (18)           |
| no   | 33 (39)           |
| you don't know   | 37 (43)           |
| Do you/ are you going to gather their opinion before vaccinating them against HPV? |                   |
| yes and you will respect it  | 22 (26)           |
| yes but you will make the final decision   | 39 (46)           |
| no   | 13 (15)           |
| you don't know   | 11 (13)           |
| totally favorable  | 23 (27)           |

(continued)

(Continued)

| Question  | Total, n=85 n (%) |
|---|-------------------|
| About vaccination in general, are you:  |                   |
| rather favorable  | 39 (46)           |
| rather not favorable  | 3 (3)             |
| not favorable   | 5 (6)             |
| no opinion  | 4 (5)             |
| it depends on which vaccine   | 11 (13)           |
| Do you think that HPV vaccination is useful?  |                   |
| yes   | 37 (43)           |
| no  | 20 (24)           |
| no opinion  | 33 (39)           |
| Do you think that it could induce severe side-back effects?   |                   |
| totally agree   | 19 (22)           |
| rather agree  | 36 (43)           |
| rather don't agree  | 7 (8)             |
| don't agree   | 4 (5)             |
| no opinion  | 19 (22)           |
| Do you fear vaccinal adjuvants?   |                   |
| yes thus you refuse vaccination   | 23 (27)           |
| yes but without calling into question vaccination   | 44 (52)           |
| no  | 9 (10,5)%         |
| no opinion  | 9 (10,5)          |
| What does your knowledge about HPV rely on?   |                   |
| media   | 29 (34)           |
| internet general websites   | 33 (39)           |
| official governmental websites  | 18 (21)           |
| forum, blog   | 9 (11)            |
| friends, family   | 17 (20)           |
| GP or gynecologist  | 41 (49)           |
| To what extent could the advice given by your general practitioner or gynecologist about HPV vaccination influence your decision? |                   |
| you follow his/her advice   | 22 (26)           |
| you agree but look for more information   | 58 (68)           |
| you don't follow the advice   | 5 (6)             |
| Has your general practitioner talked to you about HPV vaccination for your daughter?  |                   |
| yes he/she offered it   | 26 (31)           |
| yes he/she talked about it  | 8 (9)             |
| yes he/she did not recommend it   | 2 (2)             |
| no  | 49 (58)           |

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## II. MATERIEL ET METHODES

Grâce à un financement de l'ARS, nous avons monté un projet intitulé PROM SSCOL. Cette recherche a reçu l'avis favorable du Comité de Protection des personnes (CPP) de l'Ouest II d'Angers (n° 20.05.14.35227 ; 2020/46) et l'autorisation de l'Agence nationale de la sécurité du médicament (ANSM). L'étude a été enregistrée dans la base [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04459221; <https://clinicaltrials.gov/ct2/show/NCT04459221>)

Le protocole de l'étude PROM SSCOL a été publié dans : JMIR Research Protocols (Article 3).

### A. HYPOTHESES DE RECHERCHE

1. Une information claire, loyale et appropriée auprès de la population cible concernée par la vaccination (collégiens âgés de 9 à 17 ans), ainsi qu'auprès de leurs parents, permettra d'améliorer les connaissances sur l'intérêt de la vaccination en général, mais plus spécifiquement contre le HPV et ainsi d'augmenter leur adhésion à cette vaccination.
2. Une offre combinant information et réalisation de la vaccination dans le cadre scolaire permettra d'améliorer sa couverture car cela permettra de diminuer les éventuels freins matériels pouvant empêcher la démarche de vaccination.
3. Une sensibilisation des médecins généralistes leur permettra de mieux connaître les bénéfices et les risques de la vaccination contre le HPV et ainsi de favoriser l'adhésion des familles, qui leur font naturellement confiance.

## B. JUSTIFICATION DES CHOIX METHODOLOGIQUES

Cet essai monocentrique ne concernera que la zone Sud de La Réunion, l'objectif étant de répondre à une problématique locale particulière prenant en compte du tissu associatif et partenarial existant, même s'il est attendu que les résultats soient extrapolables aux autres départements français.

Dans la mesure où :

- il y a un lien objectivé entre classe socio-économique et couverture vaccinale, il a été décidé de ne faire porter l'étude que sur des collèges en Réseau d'Education Prioritaire + (REP+) qui intéressent théoriquement les populations dans lesquels les taux de couverture par la vaccination HPV sont les plus faibles.
- Afin d'éviter tout effet de « contamination » entre les 2 établissements, et dans la mesure où certains médecins généralistes pourraient prendre en charge des élèves dans les 2 collèges participants, il a été décidé de choisir 2 collèges de 2 villes distinctes

A La Réunion, 21 collèges sont classés en REP+, répartis dans 7 villes.

En accord avec le rectorat de La Réunion et les principaux des établissements, deux collèges ont été désignés parmi les collèges REP + :

- Le groupe intervention sera le collège Paul Hermann, situé à St Pierre
- Le groupe témoin sera le collège Plateau Goyave, situé à St Louis

Ce choix tient compte notamment de la disponibilité de l'établissement à accueillir une recherche clinique, de la situation géographique, de la possibilité de stationner le bus santé aux abords immédiat de l'établissement, de la zone d'intervention de l'association nous accompagnant avec un bus santé, soit dans le bassin sud de l'île. Dans chacun des 2 collèges, nous procéderons à un tirage au sort de 3 classes dans chaque section (6°, 5°, 4° et 3°) afin d'avoir des effectifs équilibrés dans chaque bras et des populations les plus comparables possibles

### C. INTERVENTIONS MENEES

Au cours de l'année scolaire 2020-2021, nous avons mené les actions suivantes dans le collège intervention :

- Cours de santé sexuelle pendant une heure de classe, avec information sur la vaccination HPV auprès des collégiens
- Une réunion d'information avec les parents devait nous permettre de présenter notre projet d'étude et de leur délivrer une information concernant la vaccination HPV. Cependant, le COVID ne nous permettant pas les rassemblements, chaque membre de l'autorité parentale des enfants concernés a été appelé pour information, et recueil du consentement oral pour la vaccination de leur enfant
- Réunion d'information pour les médecins généralistes ayant leur cabinet dans un rayon de 5km autour de l'établissement sur le thème « Autour du HPV »
- Proposition d'une vaccination anti HPV gratuite (avec le vaccin nonavalent) au sein d'un bus santé (appartenant à une Association locale, Asetis, avec des animateurs de prévention présents sur le terrain), garé dans la cour du collège. Les élèves pouvaient s'y rendre pendant la récréation ou les heures de permanence scolaire. Trois semaines de campagnes vaccinales ont été organisées au cours de l'année pour que les enfants puissent bénéficier d'un schéma vaccinal complet avec une dose à 0, 2 mois et 6 mois.
- Récupération des données vaccinales dans le carnet de santé, après recueil du consentement signé des deux parents

Ce collège intervention a été comparé à un collège témoin, où aucune action spécifique n'a été menée.

### D. OBJECTIFS DE LA RECHERCHE

#### *i. Objectif principal*

Évaluer, dans une population de collégiennes (filles) à La Réunion, l'impact du programme de promotion de la santé sexuelle et de la vaccination anti-HPV comprenant :

- l'information en milieu scolaire (élèves et parents),
- la formation des médecins généralistes,
- la proposition de la vaccination en milieu scolaire (« bus santé »),

sur la proportion des collégiennes ayant réalisé le schéma vaccinal anti-HPV complet (2 ou 3 doses), 9 mois après son initiation.

*ii. Objectifs secondaires*

Dans la population de l'étude, 9 mois après l'initiation du programme de promotion de la santé sexuelle et de la vaccination anti-HPV:

- (1) Evaluer l'impact du programme sur la proportion des collégiennes (filles) ayant initié la vaccination anti-HPV (au moins une dose),
- (2) Evaluer l'acceptabilité d'un programme de vaccination anti-HPV chez les collégiens (garçons)
- (3) Décrire les freins à la vaccination anti-HPV, chez les filles et chez les garçons,
- (4) Evaluer l'acceptabilité de la vaccination anti-HPV en milieu scolaire,
- (5) Evaluer l'intérêt de la mise en place d'un point info santé sexuelle par un bus santé,
- (6) Evaluer la satisfaction des élèves, parents et intervenants scolaires par rapport aux dispositifs mis en place.
- (7) Evaluer les taux de couverture vaccinale à jour pour les différents vaccins obligatoires, selon le calendrier vaccinal national en cours.

**Article 3.** Impact d'un programme de promotion de la vaccination contre le papillomavirus en collège : Protocole d'étude pour un essai contrôlé en cluster

Résumé

Contexte : A La Réunion, l'incidence et la mortalité du cancer du col de l'utérus sont élevées, alors que le taux de couverture de la vaccination contre le papillomavirus humain (HPV) est faible.

Objectif : L'objectif principal de l'étude est d'évaluer l'impact d'un programme de promotion de la santé et de vaccination HPV sur la proportion de collégiennes réalisant le schéma complet de vaccination HPV (2 ou 3 doses) avant la fin de l'année scolaire.

Méthodes : Cette étude est une étude de supériorité interventionnelle contrôlée en cluster. Un programme combiné de promotion de la santé sera proposé. Il comprendra des informations destinées aux élèves et aux parents, la formation de médecins généralistes et la vaccination gratuite en milieu scolaire (dans un "bus santé"). Les enfants qui participeront à ce programme constitueront le groupe d'intervention et seront comparés aux enfants d'un autre collège qui ne participeront pas au programme, constituant ainsi le groupe de contrôle.

Résultats : Le recrutement a débuté en octobre 2020. Dans l'école d'intervention, sur 780 élèves, 245 ont été tirés au sort dans 12 classes. Dans l'école témoin, ce sont 259 élèves sur 834 qui ont été tirés au sort.

Conclusions : Dans cette étude, nous explorons l'impact d'un programme de promotion de la santé combinant l'information des collégiens, leurs parents et les médecins généralistes avec une vaccination gratuite en milieu scolaire. Nous nous attendons à une couverture vaccinale HPV significativement plus élevée dans le collège intervention par rapport au collège contrôle, que ce soit chez les filles ou les garçons. L'implication finale serait une extension de ce programme dans tous les collèges de l'île et donc une augmentation de la couverture vaccinale HPV.

Protocol

# Impact of a Papillomavirus Vaccination Promotion Program in Middle School: Study Protocol for a Cluster Controlled Trial

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## Abstract

**Background:** On Reunion Island, incidence and mortality for uterine cervical cancer is high, yet coverage rate for human papillomavirus (HPV) vaccination is low.

**Objective:** The main objective of the study is to evaluate the impact of a health promotion program promoting HPV vaccination on the proportion of middle school girls who complete the full HPV vaccination schedule (2 or 3 doses) by the end of school year.

**Methods:** This study is a cluster controlled intervention study using a superiority design. A combined health promotion program will be offered containing information to students and parents, training of general practitioners, and free school-based vaccination (in a "health bus"). Children who attend this program will constitute the intervention group and will be compared to children from another middle school who will not attend the program constituting the control group.

**Results:** Recruitment began in October 2020. In the intervention school, of 780 students, 245 were randomly selected in the 12 classes. In the control school, 259 students out of 834 were randomly selected.

**Conclusions:** In this study, we explore the impact of a health promotion program combining information toward students, parents, and general practitioners with free school-based vaccination. We expect a significantly higher HPV vaccination coverage in the intervention school as compared to the control school, whether it be among girls or boys. The final implication would be an extension of this program in all middle schools on the Island and thus an increase in HPV vaccination coverage.

**Trial Registration:** ClinicalTrials.gov NCT04459221; <https://clinicaltrials.gov/ct2/show/NCT04459221>

**International Registered Report Identifier (IRRID):** DERR1-10.2196/35695

(*JMIR Res Protoc* 2022;11(6):e35695) doi: [10.2196/35695](https://doi.org/10.2196/35695)

## KEYWORDS

HPV vaccine; vaccination program; middle school; school; student; women's health; sexual health; cervical cancer; vaccination; papillomavirus; vaccine; public education; patient education; community education; promotion; program; youth; children; protocol; mortality; uterine cervical cancer; cancer; HPV; health promotion; girls; school; intervention; parent; training



## Introduction

### Background

On Reunion Island, a French territory located near the eastern coast of Madagascar in the Indian Ocean, uterine cervical cancer is the fourth most common cause of cancer in women, similar to worldwide [1]. However, the standardized incidence rate in 2016 was 8.8 in 100,000 women, 2 times higher than in metropolitan France. The standardized mortality rate follows a similar trend: on Reunion, it accounts for 4.8 in 100,000 women, whereas the metropolitan rate was 1.7 in 100,000 women [2,3].

Cervical cancer results from human papillomavirus (HPV) infection, which is the most common viral sexually transmitted infection. There are more than 100 types of HPV, some of which are high-risk oncogenes, such as HPV 16 and HPV 18, which are responsible for 70% to 80% of invasive cervical cancers [4]. On Reunion Island, most frequent HPV genotypes are HPV 16, HPV 52, HPV 33, and HPV 31, all contained in the nonavalent HPV vaccine [5].

Indeed, prevention of cervical cancer is mainly based on screening by cervical HPV test and on HPV vaccination, which has proven to be effective in reducing the prevalence of HPV transmission but also in reducing the incidence of condyloma and intermediate grade dysplasia [6,7]. Since HPV is mainly transmitted sexually, it is important to vaccinate before the beginning of sexual life.

Because HPV infections can also lead to vulvar, vaginal, penile, anal, or throat cancers, some countries (eg, United States, Canada, Australia, Germany, Austria, Belgium, Italy) recommend gender-neutral vaccination in order to promote herd immunity and reduce circulation of the virus in the general population [6,8]. In France, since December 2019, it is recommended that HPV vaccination should be offered to all children, regardless of their gender, aged 11 to 14 years (2 doses), with catch-up vaccination possible for adolescents aged 15 to 19 years not yet vaccinated (3 doses). Before December 2019, vaccination was only recommended for girls. High levels of vaccination coverage are obtained in countries that vaccinate in schools [9-11].

On Reunion Island, the HPV vaccination coverage rate is the lowest in France, estimated at 8.1% among girls aged 16 years in 2018, while the national average is already low (23.7%) [12].

This low coverage rate on Reunion Island may have several explanations. First, inhabitants seem to be poorly informed about the existence of this vaccine [13]. Moreover, vaccination coverage rates depend on the socioeconomic level of the population. In France, lower rates of HPV vaccination uptake were observed in adolescents with universal health insurance coverage (French equivalent of the US Medicaid program) compared with those not receiving such insurance [14]. Reunion Island is one of the French departments with the highest rates of inhabitants covered by this universal health insurance. Finally, not only is there vaccination hesitancy in general but also most specifically against HPV vaccine, among patients and also among physicians [13]. A total of 41% of Reunion inhabitants hold unfavorable opinions about vaccinations, with the HPV

vaccine being among the most frequently cited. Among patients not vaccinated against HPV, 37% stated that the vaccine had not been suggested to them by their doctor, and 7.3% were confronted with doubts expressed by their doctor concerning vaccination in general [13]. However, a systematic review of 79 studies in 15 countries showed that the most important factor influencing HPV vaccination was physician recommendation [15,16]. Indeed, 89.3% of the Reunion population fully trusts their doctor [13]. Therefore, interventions targeting health professionals and especially general practitioners appear to be paramount, especially when combined with interventions targeting the population to be vaccinated [17].

Thus, given the epidemiological situation on Reunion Island (high incidence and mortality for cervical cancer, very low coverage rate for HPV vaccination), we aimed to study the impact of a prevention program against sexually transmitted infections, including pathologies related to HPV, with a program promoting HPV vaccination among young students in middle school.

### Objectives

Hypotheses were as follows: (1) clear and appropriate information for the target population of the vaccination (middle school students aged 9 to 17 years) as well as for their parents will improve their knowledge about HPV vaccination and thus increase their adherence to this vaccination regimen, (2) combining information with vaccination in the school setting will improve coverage, as it will reduce any material obstacles that may prevent the vaccination process, and (3) raising awareness among general practitioners will enable them to better understand the benefits and risks of HPV vaccination and thus encourage families, who naturally trust them, to adhere to the program.

The main objective of the study is to evaluate, in a population of middle school girls on Reunion Island, the impact of a health promotion program on the proportion of middle school girls who complete the full HPV vaccination schedule (2 or 3 doses) by the end of school year.

The program, conducted during school year, will combine: (1) sexual health promotion (students and parents) during classes at school at the beginning of school year, (2) training of general practitioners (who practice in a perimeter of 5 km around the middle school) on HPV vaccination at the beginning of school year, and (3) free school-based vaccination (in a “health bus”) during the academic year.

Secondary objectives in the study population at the end of school year are as follows:

- Assess the impact of the combined health promotion program on the proportion of middle school girls who initiated HPV vaccination (at least 1 dose)
- Assess the acceptability of the HPV vaccination program among middle school boys
- Describe the barriers to HPV vaccination for both girls and boys
- Assess the acceptability of HPV vaccination in the school setting

- Assess the value of setting up a sexual health information point through a health bus
- Evaluate the satisfaction of students, parents, and school workers with the measures put into place
- Evaluate vaccination coverage for different mandatory vaccines according to the current national vaccination calendar

The aim of this study was to evaluate whether a health promotion program combining information and free school-based vaccination could raise HPV vaccination coverage.

## Methods

### Trial Design

This study is a cluster controlled intervention study using a superiority design. Children who will attend the combined health promotion program will constitute the intervention group and will be compared with children who will not attend the program (as is currently the case in all French middle schools), who will constitute the control group.

### Study Setting

This trial will concern Reunion Island in order to investigate the particular epidemiological situation of HPV on the island, even if the results of this study are expected to be applicable to other French regions.

The 2 arms of the trial will be designed to have the most comparable populations and to avoid any risk of contamination between the 2 arms or having general practitioners taking care of children in both schools.

We have thus chosen to carry out a cluster trial. The 2 groups (intervention group and control group) will be selected from a middle schools located in each of 2 cities. In each of the schools, we will randomly draw 3 classes in each grade level (6th, 7th, 8th, and 9th grade) to have a balanced number of students in each arm (see sample size). Thus, 12 classes will be selected for each school.

Provided that there is a relationship between socioeconomic status and vaccination coverage, it was decided to focus the study only on middle schools in priority education zones, which theoretically enroll a population in which HPV vaccination coverage is the lowest. On Reunion Island, 21 middle schools are classified as priority education zones, spread over 7 cities. In agreement with the head of the academy and the school directors, 2 schools have been designated among the abovementioned middle schools: the intervention school will be Paul Hermann Middle School, located in St Pierre, and the control school will be Plateau Goyave Middle School, located in St Louis.

These choices are based on the schools' ability to participate in this research, their geographical location, and the ability to park the health bus at or in the immediate surroundings of the school of the intervention group. The health bus will be provided by the Association d'Education Thérapeutique et d'Intervention Sociale (ASETIS, or Association for Therapeutic Education and Social Intervention), existing since 1996 and recognized as being of public interest.

### Eligibility Criteria

Inclusion criteria are as follows: enrolled in one of the classes randomly selected in the 2 middle schools designated, affiliated with or benefiting from a social security system, who will agree to participate in the study and whose parents or holders of parental authority will sign a free, informed, and written consent. Exclusion criteria (intervention group only) are as follows: hypersensitivity to the active substances or to one of the excipients of the vaccine (Gardasil 9), a permanent contraindication to vaccination, pregnant or breastfeeding (based on self-reporting), already initiated HPV vaccination (complete or incomplete schedule), or eligible to participate for collection of data but not for vaccination in the health bus; students with an incomplete vaccination schedule will be referred to their general practitioner to complete the missing doses. Vaccinations will be performed by a junior doctor under the supervision of a senior doctor.

### Intervention Description

#### Intervention Group

Meetings with parents in the intervention middle school will be scheduled at the beginning of school year to inform parents about HPV vaccination and explain this study to them. Consent forms will be collected during these meetings. If assemblies are forbidden by the government because of COVID-19, information meetings for parents will be cancelled. Instead, 6 interventions will be planned.

#### August-September: Program Information Sent Home to Parents via Students

Written information adapted to student age about HPV vaccination, and documents outlining objectives, interventions, constraints, foreseeable risks and expected benefits of the research, and the rights of the participants in this research context will be sent with children to give to their parents. Consent form to participate to the study to be signed by both parents or holders of parental authority and a sociodemographical questionnaire with questions about HPV knowledge will also be included.

#### October-November: Contact With Parents and Return of Information to School

Investigation team will call each authority holder individually by telephone to inform them about HPV vaccination, the study, its objective, nature of the constraints, and foreseeable risks and expected benefits of the research. The team will also remind them of the rights of participants in research and will check the eligibility criteria. Finally, when possible, the team will collect their oral consent. Parents will be asked to place the documents (consent form and sociodemographic questionnaire) in an envelope and seal it before returning it to the main teacher for reasons of data confidentiality. Documents will then be collected by the investigation team.

#### November-December: Data Collection and Student Information Sessions About Sexual Health and Vaccination

Children in the selected classes will be asked to bring in their health record on a specific date, along with the above mentioned documents, for those who forgot to return the envelope to the

main teacher previously. On that day, an investigator will collect data necessary for the study in the health records (especially vaccination data) for children for whom consent form was signed by the parents. During this time, an information session about sexually transmitted diseases and vaccination will be given in class, lasting approximately 1 hour and adapted to the level of understanding (according to grade and age), in partnership with teachers. Health records will be immediately returned to the students.

### **November-December: General Practitioner Information Dissemination**

A total of 88 general practitioners working in a radius of 5 km around Paul Hermann Middle School will be sent an information leaflet about HPV vaccination and cervical cancer prevention, including the latest literature review, and information about this study. If meetings are forbidden, general practitioners will be invited to a video conference call, "Around HPV," at the beginning of school year.

### **December, February, and May (3 Campaigns): HPV Vaccination in the Health Bus**

Free HPV vaccination will be offered in a health bus for girls and boys. The bus will be parked in the playground, inside the school grounds, allowing students to go there during breaks, lunchtime, or after school. Vaccination periods will be predefined, so that the recommended HPV vaccination schedules can be followed.

Vaccinations will be performed by the medical staff of the University Hospital of Reunion Island (a junior doctor under the supervision of a senior doctor) after informed consent to vaccination signed by either parents or holders of parental authority, who are invited to come along into the bus with their child.

Vaccination will be performed with nonavalent HPV vaccine. The proposed schedule is the one recommended by the marketing authorization: children aged 9 to 14 years (girl or boy): 2-dose schedule (intramuscular), with the second dose to be administered between 5 and 13 months after the first dose; children aged 15 years and older (girl or boy): 3-dose schedule (intramuscular), with the second dose to be administered at least 1 month after the first and the third at least 3 months after the second, with all 3 doses to be administered within 1 year. The vaccine label data will be documented in the health record.

Before vaccination, absence of contraindications will be checked. In case of high fever or acute illness, the vaccination will be postponed and offered at a later date. Vaccinated persons will be monitored for at least 15 minutes after vaccination in the presence of medical staff because of adverse effects that may occur in the direct aftermath of the injection (rare anaphylactic reactions, syncope (fainting) sometimes associated with falls) or psychogenic reaction to needle injection (neurological signs such as transient blurred vision, paresthesias, and tonic-clonic movements of the limbs during the recovery phase). During campaigns in February and May, the first dose of vaccination can be offered, although children will be asked to return to their general practitioner for subsequent doses.

The health bus system will be implemented as part of this study. Two students will be able to be vaccinated at a time. A child will never be left alone with an adult inside the bus; there will always be a minimum of 2 adults present. Students can take advantage of this special time on the bus to receive personalized information on sexuality and obtain free condoms.

### **June: Data Collection in Randomly Selected Classes**

At the end of school year (June), an investigator will collect data from health records at a specific time during class. In particular, the researcher will look for the presence of *de novo* HPV vaccination performed by general practitioners outside of the health bus. Signed consent of parents or holders of parental authority will be collected before any intervention in the study (ie, before data collection and before school vaccination is carried out).

Vaccination data, even if not collected at the time of the intervention, can be collected either during the vaccination campaigns, or during the intervention at the end of school year, especially for children whose parents have agreed to participate but not to be vaccinated in the health bus. Indeed, since vaccination dates appear in the health record, it will be possible afterward to know whether pupils were vaccinated before the interventions under study in order to have the vaccination rate at the very beginning of the study.

### **July-September: Evaluation of Satisfaction and Barriers to Vaccination**

Research staff will meet with students, parents, members of school staff, and general practitioners who volunteered, and semidirected interviews will be conducted to understand their satisfaction about the study and determine barriers to vaccination.

### **Control Group**

In the control middle school, the study will take place at the end of school year (May-June) in 2 stages.

### **Parent Information About the Study**

We will organize parent meetings to inform them of the study. If no parental meeting is possible due to the COVID-19 pandemic, parents of children in selected classes will be sent an envelope containing written information about HPV vaccination and information about the study, the sociodemographical questionnaire, and the objection form to participate to the study (data collection of health record). Thus, if the form is returned to a teacher, the investigation team will not be able to access the child's health record. On the other hand, if no form is returned, it will be considered that parents do not object to data collection.

### **Data Collection and Student Information About Sexual Health and Vaccination**

Children in the selected classes will be asked to bring in their health record on a specific date, along with the completed sociodemographic questionnaire and signed informed consent for data collection from parents. On that day, an investigator will collect data necessary for the study (especially vaccination data) in the health records for children for whom no objection form was returned. During this time, an information session

about sexually transmitted diseases and vaccination will be given in class, lasting approximately 1 hour and adapted to the level of understanding (according to grade and age), in partnership with teachers. Health records will be immediately returned to the students concerned.

### Participant Timeline

Participant timeline is displayed in Figure 1. In case assemblies are forbidden due to COVID-19 pandemic, parental meetings will be cancelled and an alternative participant timeline is displayed in Figure 2.

Figure 1. Initial participant timeline. HPV: human papillomavirus.

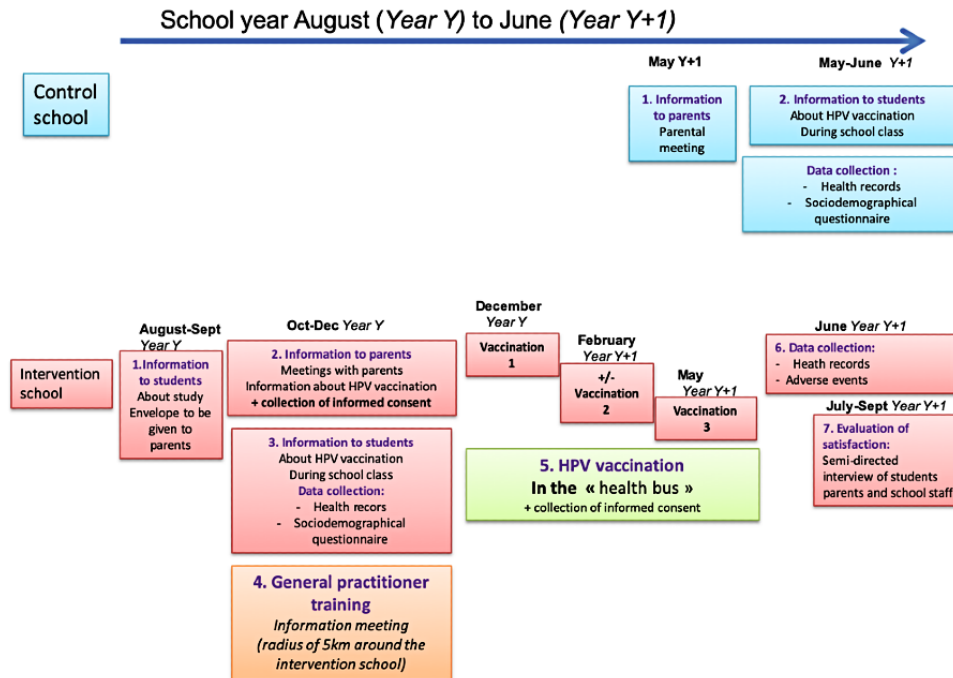
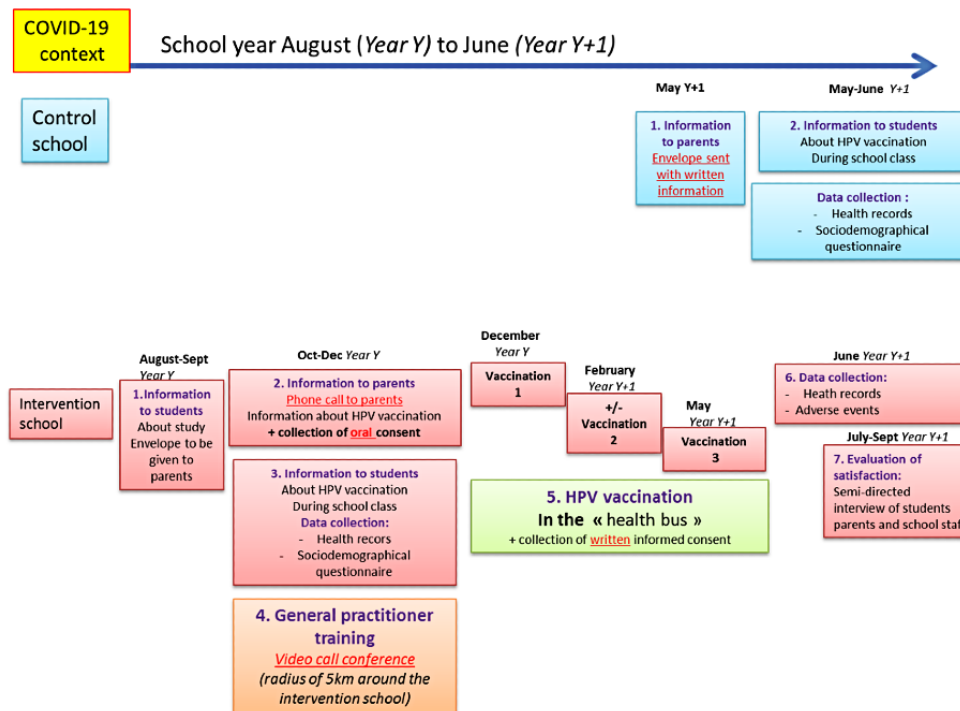


Figure 2. Participant timeline in the context of COVID-19, with meeting restrictions. HPV: human papillomavirus.



### Data Collection and Management

Data will be collected in a paper observation book after consent is signed by parents or holders of parental authority and by students. Data will be collected in the form of self-questionnaires

(parents and children). Data concerning vaccination status at inclusion and at the end of the study were checked in the health record by the investigation team.

Data will be collected in paper format and will be entered into an electronic case report form (Ennov Clinical) by a clinical



study technician. Data will be saved daily. A data validation plan, defined jointly by the principal investigator and the Methodology and Data Management Center (from the University Hospital of Reunion Island), will be developed and the controls to be performed will be described in detail for each variable. Once data entry is completed, the data will be checked for consistency. Inconsistencies will be reported in the CS Test module of Ennov Clinical. The data freeze/unfreeze process will be performed according to the procedure set up in the Methodology and Data Management Center.

### Plans for Storage of Vaccine

University Hospital of Reunion Island will be in charge of purchasing the vaccine doses and providing them, via the central pharmacy, to the ASETIS health bus at the intervention college. There will be no change in product packaging, which was identical to the packaging at the time of purchase: 0.5 mL glass prefilled syringes with needles. Labeling (in accordance with current regulations and good clinical practice) referring to use in clinical research will be affixed to the boxes of vaccines intended for the study. The products will be brought by a staff member of the ASETIS association on the days of school vaccination.

The products will be transported, respecting conditions of conservation of the vaccine (kept between 2 °C and 8 °C and protected from light). Expiration date will be checked before any injection. Accounting and traceability of the doses given will be documented by the doctors administrating the vaccination. The health bus has the capacity to store the vaccine doses in the appropriate conditions in a refrigerator.

The products will be stored at the central pharmacy in University Hospital of Reunion Island and in the health bus on vaccination days. The unused doses during the first school vaccination campaign (first dose) will be returned to the hospital central pharmacy to be used during the following campaigns. At the end of the vaccination campaigns, the unused or expired doses will be destroyed according to the regulations in force.

### Statistical Analyses

#### Sample Size

To our knowledge, there are no recent studies that have evaluated the impact of school-based vaccination on HPV vaccination coverage rates. An experimental catch-up vaccination program (diphtheria, tetanus, poliomyelitis, pertussis, measles, mumps, rubella, meningococcus C, hepatitis B, and HPV) in schools in the Vosges (Eastern France) [18] showed a participation rate ranging from 42.9% in the first year to 29% in the second year.

The calculation of the study size is based on the expected proportion of vaccination among girls, as this is the main objective of this study and we have no data for vaccination among boys at this time. Statistical assumptions were as follow:

- Proportion of schoolgirls who have had a complete HPV vaccination schedule at the end of school year of 6% in the control group for all students (compared to the 8.1% expected at age 16 years [12])

- Proportion of schoolgirls with a complete HPV vaccination schedule at the end of the school year of 20% in the intervention group

Thus, 87 girls in each group would need to be included to demonstrate this 14% difference at  $\alpha=0.05$  and power ( $1-\beta=0.80$ ). Assuming 15% nonanalyzable data (lost to follow-up, nonresponse), a total of 103 female students per group would need to be included. As there are roughly as many girls as boys in each class, we would need to include 206 students per group. In order to have an equal representation of each age group, the sampling will be stratified in the grades: 6th, 7th, 8th, and 9th grade. Thus, 52 students per grade and per group should be included.

If we consider that the classes contain an average of 22 students each, a minimum of 3 classes per grade should be randomly selected in each of the 2 middle schools to ensure the minimum necessary recruitment. Thus, randomly selecting 3 classes per grade in each of the 2 middle schools will make it possible to include approximately 132 female students per group and thus to ensure the minimum necessary recruitment. A total of 528 students are expected to be recruited (264 girls [132 per group] and 264 boys [132 per group]). The calculation of the number of subjects required was performed with PASS (version 15, NCSS) software.

#### Sequence Generation

In priority education schools, there are classes called Sections d'enseignement general et professionnel adapté (SEGPA; adapted general and vocational education sections): these classes, from 6th to 9th grade, are integrated into the middle school. They welcome young people who have significant school difficulties that cannot be resolved by academic assistance and support. There is only a small group of students (16 maximum) in each class in order to individualize each student's progress. SEGPA classes should enable students to access at least a professional qualification.

In the Paul Hermann Middle School, there are 9 classes in each grade, including 2 classes of SEGPA per grade. In the Plateau Goyave Middle School, there are 9 classes in 6th grade and 9th grade and 10 classes in 7th and 8th grade, including 2-3 classes of SEGPA per grade. In each of the selected middle schools, 12 classes will be randomly selected in order to have a balanced number of students in each arm.

In order to have an equal representation of each age group, the sampling will be stratified on the grade (6th, 7th, 8th, and 9th grade), and in order to take into account the specificities of SEGPA classes, we decided to stratify on SEGPA classes as well. As the main point in this comparative trial was similarity of the 2 groups compared, we decided to randomly select 1 SEGPA class per grade and 2 non-SEGPA classes per grade. Thus we will include in this trial 256 students from Paul Hermann Middle School (intervention group) and 255 students from Plateau Goyave Middle School (control group).

#### Statistical Methods for Primary and Secondary Outcomes

The aim of this study is to compare clinical outcomes between classes from a middle school sensitized to HPV vaccination

through a combined health promotion program (intervention group) and a middle school without any specific action (control group). The null hypothesis is that there is no difference in the groups. For descriptive analyses, qualitative variables will be described in terms of frequencies and percentages with their 95% confidence intervals; quantitative variables will be expressed in terms of means, standard deviations, and 95% confidence intervals or in terms of medians and IQRs (25th and 75th percentiles).

Comparability of groups at inclusion will be checked: bivariate comparisons of categorical variables will be performed by the chi-square test or Fisher exact test, depending on the conditions of application. Bivariate comparisons of means will be performed by the Student *t* test or Mann-Whitney *U* test, depending on the conditions of application. For the analysis of the primary outcome: the proportion of schoolgirls who will have completed the full HPV vaccination regimen at the end of the school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test, according to validity conditions.

Concerning secondary outcomes analysis: the proportion of schoolgirls who initiated HPV vaccination (1 dose) by the end of school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test according to validity conditions. The proportion of boys who will have completed the full vaccination schedule at the end of school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test, according to validity conditions. The proportion of boys who will have initiated the vaccination scheme at the end of the school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test, depending on the conditions of validity.

The analysis of barriers to vaccination will describe the causes of nonvaccination reported for students who did not initiate the vaccination schedule. Analyses will be performed for girls and boys separately. We will also compare sociodemographic data, medical history, and health care utilization data between students who initiated HPV vaccination at the end of the school year and those who did not in the intervention group. Bivariate comparisons of percentages will be performed by the chi-square test or Fisher exact test depending on validity conditions. For continuous variables, comparisons will be made using the Student *t* test or the Mann-Whitney *U* test, depending on the conditions of validity. A multivariate analysis by logistic regression will be carried out in order to take into account confounding phenomena: the variable to be explained will be the fact of having initiated vaccination at the end of the school year, and the explanatory variables entered in the model will be the variables for which the significance threshold in bivariate analysis will be  $\leq .20$ .

To be determined in the intervention group: among students who initiated HPV vaccination at the end of school year, the proportion of students who used the health bus to initiate this vaccination. Among students who completed the full vaccination schedule at the end of school year, we will determine the proportion who completed all injections on the health bus.

In the intervention group, the proportion of students who used the health bus for sexual health information will be evaluated. In the intervention group, positive and negative points reported by students, their parents, and school staff about this program will be described. Proportion of students up to date for each type of vaccine (according to current vaccination calendar) at the end of school year, in the entire study population as well as in each of the 2 groups (intervention and control), and comparison of these proportions between the 2 groups by the chi-square test or Fisher exact test will be determined, according to validity conditions.

Analyses comparing control group to intervention group will all be performed on an intention-to-treat basis. All hypotheses will be tested with bilateral tests and  $\alpha=.05$  and confidence interval calculated at 95%. Analyses will be performed using SAS (version 9.4, SAS Institute Inc) software.

### Ethical Considerations

The sponsor and investigators agree that this research will be conducted in accordance with the law no. 2012-300 of March 5, 2012, relating to research involving human persons; Good Clinical Practices (version 4 of November 9, 2016, and decision of November 24, 2006); and the Declaration of Helsinki [19]. The research is conducted in accordance with this protocol. Except in emergency situations requiring the implementation of specific therapeutic procedures, the investigators undertake to comply with the protocol in all respects, in particular with regard to the collection of consent and the notification and follow-up of serious adverse events.

This research has received the favorable opinion of the research ethics committee (Comité de Protection des personnes (CPP); ethics committee for the protection of individuals) of Ouest II of Angers (No. 20.05.14.35227; 2020/46) and the authorization of the Agence nationale de la sécurité du médicament (ANSM), the French equivalent of the US Food and Drug Administration. The University Hospital of Reunion Island, promotor of this research, has taken out a civil liability insurance policy with the hospital insurance company Société hospitalière d'assurance mutuelle (no. 158958) in accordance with the provisions of the public health code.

The data recorded during this research are subject to computerized processing at the University Hospital of Reunion Island, responsible for data processing in compliance with the law no. 78-17 of January 6, 1978, relating to data processing, files, and freedoms modified by the law 2004-801 of August 6, 2004 and modified by the law no. 2018-493 of June 20, 2018. This research falls within the framework of the reference methodology (RM-001) in application of the provisions of Article 54 paragraph 5 of the amended Act of January 6, 1978, relating to information, files, and freedoms. This change was approved by decision of January 5, 2006, updated on July 21, 2016. The University Hospital of Reunion Island, responsible for data processing, has signed a commitment to comply with this reference methodology. The research sponsor undertakes to carry out the research in compliance with the General Data Protection Regulation of April 27, 2016, implemented on May 25, 2018. This research is registered in the ANSM European Union Drug Regulating Authorities Clinical Trials Database

[73-2020] and at ClinicalTrials.gov [NCT04459221]. Authors obtained consent to participate in the study from participants and their parents (or holders of parental authority). Written, informed consent to participate was obtained from all participants.

### Availability of Data and Materials

The following documents relating to the research are archived by the investigator in accordance with Good Clinical Practice for a period of 15 years following the end of the research (research involving drugs, medical devices, or in vitro diagnostic medical devices or research not involving a product mentioned in article L.5311-1 of the public health code): the protocol and any amendments to the protocol, observation notebooks (copies), the source files of participants who have signed a consent form, and all other documents and letters related to the research.

Original copies of signed informed consents from participants and authority holders will be archived for a period of 30 years following the end of the research. All of these documents are the responsibility of the investigator for the regulatory archiving period. No movement or destruction will be made without the sponsor's approval. At the end of the regulatory retention period, the sponsor will be consulted for destruction. All data, documents, and reports are subject to audit or inspection.

Within 1 year of the completion or termination of the research, a final report will be prepared and signed by the sponsor and investigator. This report will be made available to the competent authority. The sponsor will transmit the results of the research to the CPP and, if necessary, to the ANSM in the form of a summary of the final report within 1 year of the end of the research. The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

## Results

This study was funded in September 2019. Recruitment began in October 2020 (Figure 3). Concerning vaccination, recruitment was completed by June 2021. Concerning evaluation of satisfaction of participants and evaluation of barriers to HPV vaccination, completion of recruitment was completed by December 2021.

In the intervention school, of 780 students, 245 were randomly selected in the 12 classes. In the control school, 259 students out of 834 were randomly selected. Analyses are still ongoing, though it seems that this health promotion program offering information to students, parents, and general practitioners and free school-based vaccination had a positive impact on the intervention school and drew many students into the health bus for HPV vaccination.

Figure 3. Intervention screenshots.



## Discussion

### Principal Findings

In this study, we expect significantly higher HPV vaccination coverage (full vaccination or first dose) in the intervention school as compared to the control school, whether it be among girls or boys.

### Comparison With Prior Work

Previous studies have already shown the benefits of school-based educational sessions to improve adolescent knowledge and behavior regarding HPV prevention and increase the likelihood of the students to become vaccinated [20,21]. Education interventions represent a simple yet potentially effective strategy for increasing HPV vaccination, especially when targeting groups influential to the HPV vaccination behaviors of adolescents: parents [22], school staff [23], and



health care professionals [24]. Indeed, knowledge was associated with recommendation intention and behavior.

### Strengths and Limitations

This protocol is submitted more than a year after recruitment began, since sanitary COVID-19 condition was in constant change and evolution and it was difficult to know whether we could continue the process of the trial. Amendments were made and submitted to the ethics committee, facing prohibition of meetings with more than 6 people. This protocol is the result of our constant adaptation to these different obstacles.

Having different exclusion criteria for participants in the intervention and control arms may introduce a selection bias by design. However, we wanted to include as many children as possible in the control group to have a representative sample of the population, and the groups may still be comparable. The sample size calculation has not taken into account correlation between participants in the same cluster. As such, the sample size is likely to be too small. However, one limit is the price of the vaccine, which limited our ability to include more students, with regard to the funds allocated.

On Reunion Island, specificities regarding economic and societal development are as follows: high rate of universal health insurance coverage where the high cost of HPV vaccine may be a barrier, mixed culture with religious faith incompatible with premarital sex and racist biopolitical mistrust of the West from which the vaccine comes from, and the particular weight of the antivaccine leagues which casted a negative halo around the subject [25]. Thus we expect a strong veto from parents.

### Future Directions

Analysis of satisfaction and specific barriers to vaccination in this school-based design will help us improve our program. Maybe on Reunion Island, with a population with early sexual life and a high rate of adolescent pregnancy (5%) [26], the target age of HPV vaccination should be reconsidered. The final implication would be an extension of this program in all middle schools on the island and an increase in HPV vaccination coverage. These results are promising and may be a stepping stone to expand this program to the whole Reunion Island and hopefully someday decrease the burden of cervical cancer.

### Acknowledgments

Members of medical research unit of University Hospital of Reunion Island: Lucie Auzanneau, Mélanie Begorre, who provided substantial help in protocol submission to competent authorities, and Julie Ruiz, for data collection. ASETIS association, with its health bus and prevention animators, in whom children trusted to ask for information concerning sexuality and vaccination: Maryse Picard, Stéphanie Gonthier, Julianna Danessinga, Pierre Riviere, Fabrice Fontaine. Junior Doctors Xavier Gilhard, Morgane Humbert, Julien Sitthisone, and Eva Mondon, who vaccinated children in the health bus. Agence de Santé Océan Indien provided a grant to cover all the costs related to this study, including vaccine purchase. The funding body did not play any role in the design of the study, collection, analysis, interpretation of data, or writing the manuscript.

### Authors' Contributions

PLT is the chief investigator, she conceived the study, obtained financing, and led the proposal and protocol development. EC assisted in protocol development and was the lead trial methodologist. MB assisted in the development of the proposal. AB contributed to the study design and substantively revised the protocol. All authors read and approved the final manuscript.

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Peer review report.

[\[PDF File \(Adobe PDF File\), 154 KB-Multimedia Appendix 1\]](#)

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## Abbreviations

**ANSM:** Agence nationale de la sécurité du médicament

**ASETIS:** Association d'Education Thérapeutique et d'Intervention Sociale

**CPP:** Comité de Protection des personnes

**HPV:** human papillomavirus

**SEGPA:** Sections d'enseignement general et professionnel adapté

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### III. RESULTATS

Sur les 780 élèves du collèges interventions, 245 ont été tirés au sort au sein de 12 classes réparties du niveau 6<sup>e</sup> à 3<sup>e</sup>. Dans le collège témoin, 259 élèves ont été tirés au sort parmi 834 élèves.

L'objectif principal était l'évaluation de l'impact d'un programme de promotion de la santé sexuelle et de la vaccination anti-HPV sur la proportion des collégiennes ayant réalisé le schéma vaccinal anti-HPV complet à la fin de l'année scolaire.

Nos résultats montrent une augmentation significative de couverture vaccinale avec un schéma complet dans le collège où le programme de santé a eu lieu, comparativement au collège témoin (26 vs. 3 filles,  $p < 10^{-3}$ ) (Article 4).

Le nombre de vaccinations initiées était également plus élevé dans le groupe d'intervention (31 filles contre 6 filles dans le groupe témoin,  $p < 10^{-3}$ ). Les mêmes résultats ont été obtenus pour les garçons pour le schéma complet ou partiel (7 garçons contre 0,  $p = 0,01$  ; 16 garçons contre 1,  $p < 10^{-3}$ , respectivement).

A la fin de l'année scolaire, 19.2% (47/245) des enfants du collège intervention avaient bénéficié d'au moins une dose de vaccin. Parmi eux, 55.3% (26/47) ont bénéficié d'au moins une dose au sein du bus santé, montrant une acceptabilité de ce dispositif au sein de leur environnement scolaire.

Par ailleurs, les élèves étaient globalement à jour de leurs autres vaccins obligatoires.

Malgré ces résultats encourageants, le taux de participation des élèves était décevant, en dépit de nos efforts tout au long de l'année scolaire pour les sensibiliser sur l'importance de cette vaccination HPV.

Pour répondre à un des objectifs secondaires, qui était de décrire les freins à la vaccination anti HPV, nous avons mené en parallèle une étude qualitative (Article 5). Des entretiens semi-structurés en face à face, ont été menés auprès des enfants, des parents d'enfants, du personnel de l'école, des médecins généralistes, des membres

de l'association Asetis pour obtenir une compréhension approfondie des questions relatives à la vaccination contre le HPV.

Nous avons ainsi mis en évidence : la crainte d'effets indésirables graves par manque d'informations et de connaissances, la méfiance envers les scientifiques et l'industrie pharmaceutique, l'importance des fakenews relayées par les réseaux sociaux. Nous avons aussi objectivé le tabou important lié à la sexualité, relative à la transmission du HPV. Cette sexualité était associée à la peur de grossesses chez les adolescentes, dont le taux est élevé à La Réunion. L'école, les médecins généralistes, les témoignages contés et la chasse à la notoriété à la télévision (venue nous interviewer lors d'une campagne vaccinale), ont joué un rôle central pour inverser la balance et motiver la vaccination des enfants.

Il faut encourager le dialogue entre les enfants et leur réseau social proche. Pour cela, le point info santé sexuelle mis en place autour du bus santé, avec des ateliers menés par les animateurs de prévention en santé, était un atout pour distribuer une information loyale, au décours d'ateliers de coloriage. Ce dispositif a entraîné une satisfaction globale de tous les intervenants (enfants, parents, personnel enseignant).

Une des classes du collège, guidée tout au long de l'année par leur professeur principal et des membres du CRCDC (Centres régionaux de coordination des dépistages des cancers), a même participé à une campagne d'empowerment, avec création d'un poster de promotion de la santé en général à destination des cabinets de médecins généralistes de l'île.

Par rapport au groupe ayant bénéficié d'une information passive pendant une heure de classe, le taux d'étudiants ayant l'intention de se faire vacciner contre le HPV était significativement plus élevé dans le groupe participant à la campagne d'empowerment (RR 2,6 [1,9-3,5],  $p < 0,001$ ) et dans le groupe participant aux ateliers de coloriage autour du bus (RR 1,6 [1,2-2,0],  $p < 0,001$ ) (Article 6).

**Article 4.** PROM SSCOL – Impact d'un programme de vaccination contre le papillomavirus en collège pour augmenter la couverture vaccinale à La Réunion

Résumé

Contexte

A La Réunion, le cancer du col de l'utérus est la troisième cause de cancer chez la femme. La prévention primaire repose sur la vaccination contre le HPV, mais le taux de couverture est faible (8,1%). L'objectif de l'étude était d'évaluer l'impact d'un programme de promotion de la santé sur la proportion de collégiennes ayant suivi le calendrier de vaccination contre le HPV.

Méthodes

Dans cette étude interventionnelle prospective et contrôlée de supériorité, 12 classes ont été tirées au sort dans une école d'intervention où le programme de promotion a eu lieu, et dans une école témoin où aucune intervention spécifique n'était prévue. Le programme combinait : information des élèves pendant les cours, information des parents par lettre et appels téléphoniques, information des médecins généralistes par lettre et vidéoconférence, vaccination gratuite à l'école (dans un " bus santé " garé dans la cour de l'école) avec le vaccin nonavalent contre le HPV.

Résultats



Dans le groupe d'intervention, 26 filles ont bénéficié d'une vaccination complète, ce qui est significativement plus élevé que dans le groupe témoin (3 filles,  $p < 10^{-3}$ ). Le nombre de vaccinations initiées était également plus élevé dans le groupe d'intervention (31 filles contre 6 filles dans le groupe témoin,  $p < 10^{-3}$ ). Les mêmes résultats ont été obtenus pour les garçons pour le schéma complet ou partiel (7 garçons contre 0,  $p = 0,01$  ; 16 garçons contre 1,  $p < 10^{-3}$ , respectivement).

Interprétation

La mise en œuvre d'un programme de promotion de la santé et l'offre d'une vaccination gratuite en milieu scolaire ont permis d'augmenter la couverture vaccinale. Ces résultats sont prometteurs et peuvent constituer un tremplin pour étendre ce programme à l'ensemble de l'île de La Réunion et espérer un jour diminuer le poids du cancer du col de l'utérus.

## Article

# PROM SSCOL—Impact of a Papillomavirus Vaccination Promotion Program in Middle Schools to Raise the Vaccinal Coverage on Reunion Island

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**Abstract:** Introduction: On Reunion Island, cervical cancer is the third most common cause of cancer in women. Primary prevention is based on the HPV vaccination, yet coverage rate is low (8.1%). The objective of the study was to evaluate the impact of a health promotion program on the proportion of middle school girls who have completed the HPV vaccination schedule. Material and methods: In this prospective, controlled intervention study of superiority, 12 classes were randomly selected in an intervention school where the promotion program took place, and in a control school where no specific intervention was planned. The program combined: information to students during school classes, information to parents by letter and phone calls, information to general practitioners by letter and video conference call, and the free school-based vaccination (in a “health bus” parked in the schoolyard) with the nonavalent HPV vaccine. Results: In the intervention group, the completion was achieved for 26 girls, which was significantly higher than in the control group (three girls,  $p < 10^{-3}$ ). The initiated vaccination was also higher in the intervention group (31 girls vs. 6 girls in the control group,  $p < 10^{-3}$ ). The same results were obtained for the boys as for the full or partial scheme (seven boys vs. 0,  $p = 0.01$ ; 16 boys vs. 1,  $p < 10^{-3}$ , respectively). Conclusions: Implementing a health promotion program and offering the free, school-based vaccination raised the vaccination coverage. These results are promising and may be a stepping stone to expanding this program to the whole Reunion Island and hopefully someday decrease the burden of cervical cancer.

**Keywords:** HPV vaccination; middle school; health program



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## 1. Introduction

On Reunion Island (a French overseas territory located near the eastern coast of Madagascar, in the Indian Ocean), uterine cervical cancer is the fourth most common cause of cancer in women. The standardized mortality rate accounts for 4.8 in 100,000 women, three times higher than on mainland France [1,2].

CC results from the human papillomavirus (HPV) infection. The primary prevention is based on the HPV vaccination, which has proven to be effective in reducing the prevalence of HPV carriage, and the incidence of condyloma or intermediate grade cervical dysplasia [3,4], and invasive CC [5]. Thus, in Australia, where the HPV vaccination coverage is high, the incidence rate of CC could decline to less than 1/100,000 PY, by 2066 [6].

In France, before December 2019, the HPV vaccination was recommended for girls only. Since HPV infections can also lead to vulvar, vaginal, penile, anal or oropharyngeal cancers, France now recommends a gender-neutral vaccination, in order to promote herd immunity and reduce the circulation of the virus in the general population [3,7]. Because HPV is mainly transmitted sexually, it is important to vaccinate at young age. Vaccination is recommended for adolescents aged 11 to 14 years (two doses), with a catch-up vaccination possible between 15 and 19 years of age (three doses). High levels of vaccination coverage are obtained in countries that vaccinate in schools [8–10].

On Reunion Island, the HPV vaccination coverage rate is the lowest in France, estimated at 8.1% among 16-year-old girls in 2018, while the national average is already low (23.7%) [11]; yet 96.8% of the genotypes circulating on the Island are covered by the non-valent vaccine [12]. Through questionnaires to mothers and general practitioners (GPs), it appeared that a lack of information and the vaccination mistrust from parents, as well as from GPs, are the main factors contributing to the low HPV vaccination coverage [13]. Inhabitants were poorly informed about the existence of this vaccine [13], reinforced by general practitioners' doubts in whom patients trust [14]. Moreover, the vaccination coverage rates depend on the socioeconomic level of the population [15], and Reunion Island is one of the poorest French departments [16]. Therefore, given the epidemiological situation in Reunion Island (a high incidence and mortality for CC, a very low coverage rate for the HPV vaccination), interventions targeting health professionals appear to be paramount, especially when combined with interventions targeting the population to be vaccinated and their parents [17].

We conducted our study soon after the French recommendations for the gender neutral HPV vaccination, and since the acceptability of the vaccination in boys had not yet been explored, we decided to evaluate girls and boys, separately.

Thus the main objective of the study was to evaluate, in a population of middle school girls on Reunion Island, the impact of a health promotion program, on the proportion of middle school girls who have completed the full HPV vaccination schedule (two or three doses), by the end of the school year.

## 2. Material and Methods

### 2.1. Setting and Study Design

The full protocol of this prospective, controlled intervention study of superiority is available [18].

The two groups (intervention group and control group) were selected from two middle schools in Southern Reunion Island located in the priority education zone (which theoretically concerns populations with a low socio economic status).

In order to have the most comparable populations in the two arms, we carried out a cluster trial. In each of the schools, we randomly drew three classes in each grade level (6th, 7th, 8th, and 9th grade) to have a balanced number of students in each arm. Thus, 12 classes were selected from each school.

In the intervention group, a health promotion program was conducted during the 2020–2021 academic year (October 2020 to June 2021), combining information to students during school classes, information to parents by letter and phone calls, information to general practitioners by letter and video conference call, and a free school-based vaccination (in a “health bus”) with the nonavalent HPV vaccine.

Children in the selected classes were asked to bring in their health record on a specific date. On that day, an investigator collected the data in the health records. During this time, an information session about the anatomy of the genital organs, sexually transmitted diseases and vaccination was given in class, lasting approximately one hour and adapted to the level of understanding (according to grade and age), in partnership with teachers. Health records were immediately returned to the students.

Each child was given an envelope to take home, with a consent form to participate in the study to be signed (by the child him/herself and both parents or holders of parental



authority). There was also an information letter, explaining the benefits of the HPV vaccination. Since assemblies and parental meetings were forbidden during the COVID-19 pandemic, parents were phoned and oral consent was collected. During the phone calls, oral information about the HPV vaccination was delivered.

In the control group, no specific intervention was planned.

## 2.2. Objectives

The main objective of the study was to evaluate, in a population of middle school girls on Reunion Island, the impact of a health promotion program, on the proportion of middle school girls who have completed the full HPV vaccination schedule (two or three doses) by the end of the school year.

Secondary objectives in the study population at the end of school year were:

- (1) to assess the impact of the combined health promotion program on the proportion of middle school girls who initiated the HPV vaccination (at least one dose),
- (2) to assess the impact of this program among middle school boys (full schedule and initiated vaccination),
- (3) to assess the acceptability of the HPV vaccination in a school setting.

## 2.3. Data Collection

The data were collected after consent was signed by parents or holders of parental authority, and by the students. The data were collected in the form of self-questionnaires (parents and children), evaluating the socioeconomical data, and prior knowledge and acceptance of the HPV vaccination. The data concerning the vaccination status at the inclusion and at the end of the study were checked in the health record by the investigation team. The data were collected in paper format and were then entered into an electronic case report form (Ennov Clinical) by a clinical study technician.

## 2.4. Statistical Analysis

The qualitative variables were expressed as numbers and percentages with their 95% confidence interval, the quantitative variables as mean with their standard deviation (SD) or median with the 25th and 75th percentile. For the qualitative data, the intervention and control groups were compared by the Chi<sup>2</sup> test or Fisher's exact test, according to the validity conditions. Comparisons of the continuous variables were performed by Student's *t* test or the Wilcoxon test, as appropriate. The analyses were performed on an intention-to-treat basis. The hypotheses were tested with an alpha risk of 0.05, and the confidence intervals were calculated at 95%. All statistical analyses were performed using STATA SE V16<sup>®</sup> software (StataCorp, College Station, TX, USA).

## 2.5. Ethical Considerations

This research has received the favorable opinion of the research ethics committee (Comité de Protection des personnes (CPP); ethics committee for the protection of individuals) of Ouest II of Angers (No. 20.05.14.35227; 2020/46) and the authorization of the Agence nationale de la sécurité du médicament (ANSM).

## 3. Results

As exposed in the flow chart in Figure 1, the twelve classes randomly selected in each school concerned 245 students in the intervention group (108 girls with a mean age of 12.2 years (CI95%: [11.8; 12.6]) and 137 boys with a mean age of 12.3 years (CI95%: [11.9; 12.7]) and 259 in the control group (125 girls with a mean age of 12.2 years (CI95%: [11.8; 12.7]) and 134 boys with a mean age of 11.9 years (CI95%: [11.5; 12.3])). The repartition among grades 6 to 9 was similar in both groups ( $p = 0.8$ ). The health information, including vaccine status, could be collected for 36.3% (89/245) of the students in the intervention group and 33.6% (87/259) students in the control group ( $p = 0.5$ ). For students for whom the medical information were available, both groups were not significantly



different, in terms of age, gender, grade and vaccination status for vaccinations other than HPV (Table 1).

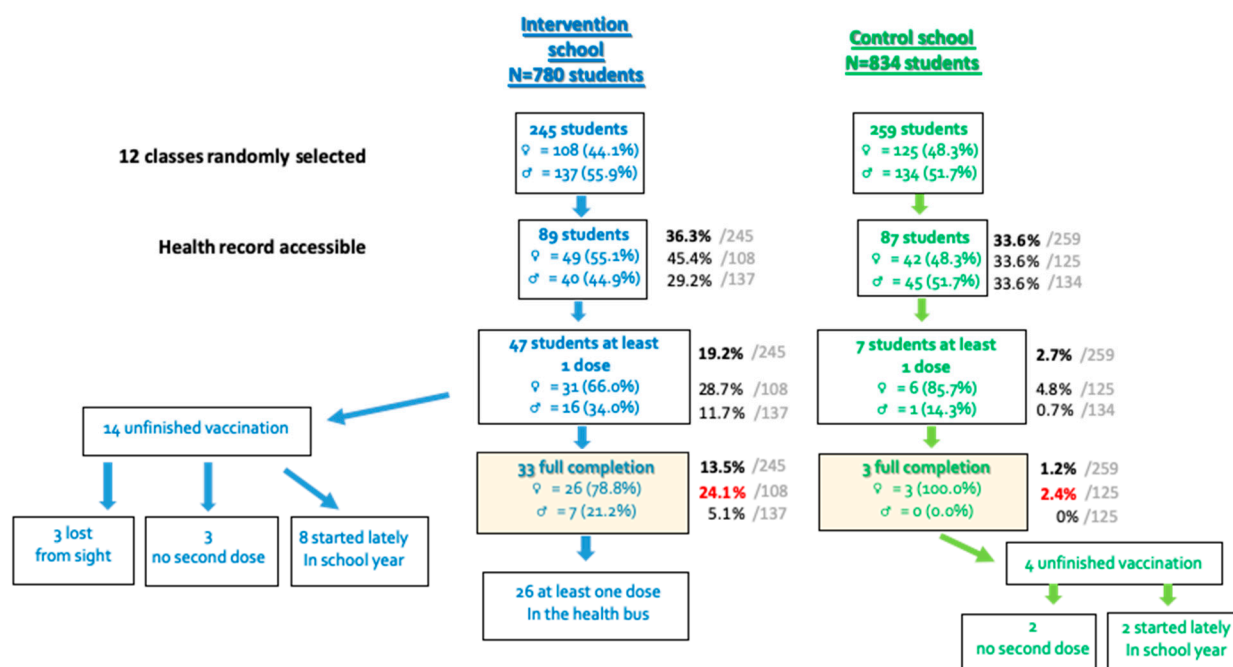


Figure 1. Flow chart. ♀: girls, ♂: boys.

Table 1. Characteristics of children for whom health records were accessible.

|  |                 | Intervention School | Control School |                 |
|--|-----------------|---------------------|----------------|-----------------|
|  |                 | N = 89              | N = 87         | <i>p</i> -Value |
|  |                 | N (%)               | N (%)          |                 |
| Age  | 9–12 years old  | 54 (60.7)           | 55 (63.2)      | 0.7             |
|  | 13–16 years old | 35 (39.3)           | 32 (36.8)      |                 |
| Gender   | Female          | 49 (55.1)           | 42 (48.3)      | 0.3             |
|  | Male            | 40 (44.9)           | 45 (51.7)      |                 |
| Grade  | 6th–7th         | 49 (44.9)           | 56 (35.6)      | 0.2             |
|  | 8th–9th         | 40 (44.9)           | 31 (64.4)      |                 |
| Up-to-date vaccinations except HPV vaccination * | yes             | 50 (41.9)           | 56 (35.6)      | 0.4             |
|  | no              | 36 (58.1)           | 31 (64.4)      |                 |

\* according to the vaccination schedule in force in France. HPV = human papillomavirus.

Of 245 children in the intervention group, some only had one holder of parental authority. For those who had both parents, we tried to call both parents, but when one of them was not available, we considered one oral consent was sufficient. However, both parents' written consent was necessary. Among 199 mothers who picked up the phone, 79 gave their oral consent for their child's vaccination. Among the fathers, 39 gave their oral consent for the vaccination among 113 who answered the phone.

A full vaccination was achieved for 24.1% of the 108 girls included in the intervention group (26 girls) by the end of the school year, which was significantly higher than the 2.4% in the control group (three girls;  $p < 10^{-3}$ ). When comparing the students with at least one HPV vaccinal dose (initiated vaccination), a higher rate was also obtained in the intervention group (31 girls = 28.7%) than in the control group (six girls = 4.8%;  $p < 10^{-3}$ ). Similar results were obtained for boys: full vaccination or initiated vaccination

rates were superior in the intervention group (5.1% vs. 0%,  $p = 0.01$ , and 11.7% vs. 0.7%,  $p < 10^{-3}$ , respectively).

HPV vaccination was initiated for a total of 47 (19.2%) students in the intervention group and 7 (2.7%) in the control group ( $p < 10^{-3}$ ). Among the 47 vaccinated children in the intervention group, 37 (78.7%) received at least one dose in the health bus that was parked in their school. Of the 33 fully vaccinated students, 26 (78.8%) received their whole scheme vaccination in the health bus. Of these children vaccinated in the bus, three adverse reactions were reported: one vagal discomfort, two with pain at the injection site, including one who felt dizziness and one who had swelling on the injection site. Concerning the 14 children with an incomplete vaccination at the end of the follow up, eight had initiated their vaccination too late, in regards to the end date of the study in order to have a complete scheme.

At the beginning of the study, 120 general practitioners located around the intervention middle school were sent an information leaflet about the HPV vaccination and were invited to participate in a video conference call about HPV. Seven health professionals participated to the conference.

#### 4. Discussion

In a population of middle school students, we implemented a health promotion program during one school year, combining students, parents and general practitioners and provided them with information about the HPV vaccination and the free school-based vaccination in a “health bus”. This intervention significantly increased the HPV vaccination coverage (full vaccination or first dose) in both girls and boys, compared to a control school.

Previous studies have already shown the benefits of school-based educational sessions to improve adolescents’ knowledge and thus their behavior regarding the HPV prevention and to increase the likelihood of the students to become vaccinated [19,20]. Education interventions represent a simple yet potentially effective strategy for increasing the HPV vaccination, especially when targeting groups influential to the HPV vaccination behaviors of adolescents: parents [21], school staff [22] and health care professional [23]. Indeed, knowledge was associated with the recommendation intention and behavior.

In similar studies in the literature, the baseline initiation and completion of the HPV vaccination rates were higher than in our population (baseline: 2.9% on Reunion Island vs. 46.7–93.9% among girls in Canada [24], 76% in New York [25], 16.1% in Sao Paulo [26]). However, the percentage increase points were very heterogenous among the studies (16.3% in Reunion, 2.9% in New York, 34.4% in Sao Paulo). Thus, the impact of these interventions appears to be greater when the baseline vaccination coverage is low.

Most vaccinations identified during the school year, were conducted in the health bus in the intervention school. In other studies, the delivery of the program occurred twice a year to provide both doses in local schools, or nurses went into schools three times a year to deliver the doses. It was perceived that offering the vaccine in schools increased accessibility and convenience [27].

The HPV vaccination coverage achieved at the end of our study was lower than expected, but among a population known to particularly mistrust the HPV vaccination [13], these results may raise hopes for the future, slowly leading to a snowball process. Indeed, children from other classes came nearby the bus during break time, seeking for information about the HPV vaccination, and 30 prescriptions were delivered for these children. Thus, the nearest pharmacy from the intervention school sold 52 HPV doses to 44 children between October 2020 and June 2021, which was two times higher than during the same period the previous year.

This reluctance to the vaccination in France was once more highlighted during the coronavirus pandemic [28]: a high vaccination coverage was slower to achieve than in more compliant Asian countries.

### *Strengths and Limits*

The strength of this study is its methodology with the randomized selection of school classes and the collection of both parental consent.

Even though our results were significant, the main limitation was the low number of participants, whether it be students (an overall participation rate of 34.9%), or health professionals invited to attend the conference (7/120). This low adherence in the conference could reflect a lack of interest and thus of the prescription of the HPV vaccination. Yet, as mentioned earlier, patients have a deep trust in their general practitioner and the doctor needs to be convinced himself in order to convince the patient and parents. Improvements are needed to sensitize healthcare professionals.

During the study, we were confronted with several difficulties: (i) we encountered great difficulties in obtaining the signed parental consents for the children's vaccination. Indeed, each child was given an envelope containing information and formalities related to the study, socio-economic questionnaires, etc. [18]. This was probably difficult to understand in a population where illiteracy reaches 23% (two times higher than in Metropolitan France) [29]. However, these logistical barriers, including getting the consent forms returned, the competing priorities within the school setting, have already been identified [27]. Of note, in a similar study conducted in Brazil, when the HPV school base vaccination was implemented, the coverage of the first dose increased from 16.1% to 50.5% ( $p < 0.0001$ ). Nonetheless, according to the Brazilian legislation for the vaccination of children, the vaccines on the National Program of Immunization list do not need the authorization from parents or guardians [26]. (ii) The COVID-19 pandemic, with the impossibility to organize in person meetings with parents and general practitioners, to convince them about the benefits of the vaccine. Moreover, it created a confusing environment between Covid and the HPV vaccine.

Qualitative interviews were conducted to evaluate the barriers to the HPV vaccination in this population, yet sensitized all along school year about its benefits (personal data).

It would have been interesting to evaluate each action separately (information VS free vaccination at school VS control), even though those actions are complementary.

Even though unlikely, students could have accepted to be vaccinated because they wanted to help the researchers and not because they were motivated by the information provided. On the contrary, the wide time offered between the first and last vaccination campaign (December to June), could have been a cause of a low adherence to the second dose. The external validity is needed by extending this program throughout Reunion Island. Since the World Health Organization seems to say that one vaccinal dose may be sufficient, maybe only one-single vaccination campaign may be required.

### **5. Conclusions**

In conclusion, implementing a health promotion program combining students information during school classes, parents and general practitioners information, and offering a free school-based vaccination on Reunion Island, could raise the vaccination coverage and hopefully someday decrease the burden of condylomas, cervical dysplasia and cancer and other HPV-induced cancers. This conclusion is not new, however it underlines the effective strategies to increase the vaccination coverage in regions with a low adherence.

Barriers to students' participation, should be understood and discarded before expanding the program to the whole Reunion Island, or even to other regions of the world.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board (or Ethics Committee) of Ouest II Angers, Maison de la recherche Clinique, CHU Angers, 49933 Angers cedex 9 (protocole code 20.05.14.35227 (2020/46), date of approval 24 July 2020).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study and their parents or holders of parental authority.

**Data Availability Statement:** Data supporting reported results are accessible upon request to corresponding author.

**Trial Registration:** [ClinicalTrials.gov](https://clinicaltrials.gov) ID: NCT04459221. ANSM EUDRACT database registration: n° 2020-002332-73.

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**Article 5.** Freins et motivations à la vaccination contre le papillomavirus en collège à La Réunion

Résumé

**Contexte.** A La Réunion, la couverture vaccinale contre les papillomavirus (HPV) est faible. Une étude encourageant la vaccination au collège, a montré un faible taux de participation. L'objectif principal de cette étude était de comprendre les barrières et les motivations à la vaccination HPV dans des populations pourtant sensibilisées à ses bénéfices.

**Méthodes.** L'étude a été menée auprès de la population autour de l'école d'intervention où le programme de promotion de la santé a été mené durant l'année scolaire 2020-2021. Des entretiens semi-structurés en face à face, ont été menés auprès des enfants, des parents d'enfants, du personnel de l'école, des médecins généralistes, des membres d'associations. Une étude qualitative a été adoptée en utilisant une approche de théorie ancrée pour obtenir une compréhension approfondie des questions relatives à la vaccination contre le HPV.

**Résultats.** Au total, 19 membres du personnel scolaire, 20 parents d'élèves du collège, 39 enfants, 5 médecins généralistes et 3 membres d'associations ont été interrogés en mai 2021. Les attitudes anti-vaccination pouvaient s'expliquer par : la crainte d'effets indésirables graves par manque d'informations et de connaissances, la méfiance envers les scientifiques et l'industrie pharmaceutique, l'importance des fakenews relayées par les réseaux sociaux. L'école, les médecins généralistes, les témoignages contés et la chasse à la notoriété à la télévision, ont joué un rôle central pour inverser la balance et motiver la vaccination des enfants.

**Interprétation.** La spécificité de notre population était la peur de la grossesse chez les adolescentes, dont le taux est élevé à La Réunion. Il faut lever ce tabou lié à la sexualité et encourager le dialogue entre les enfants et leur réseau social proche. Cette meilleure compréhension des barrières et des motivations permettra de trouver des solutions pour étendre ce programme de promotion de la vaccination HPV à toute l'île de La Réunion.



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Understanding barriers and motivations to Papillomavirus vaccination in a middleschool in Reunion Island

--Manuscript Draft--

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| <b>Abstract:</b>                    | <p>Background</p> <p>In Reunion Island, papillomavirus (HPV) vaccination coverage is low. A study encouraging vaccination in middle school, showed low rate of participation. The main objective of the study was to understand barriers and motivations to HPV vaccination in populations yet sensitized to its benefits.</p> <p>Methods</p> <p>The study was conducted among the population around the intervention school where the health promotion program was conducted during school year 2020-2021. Semi-structured face-to-face interviews, were conducted among children, children's parents, school staff, general practitioners, association members. A qualitative study was adopted using a grounded theory approach to obtain an indepth understanding of issues pertaining to HPV vaccination.</p> <p>Findings</p> <p>A total of 19 school staff members, 20 parents of middle school children, 39 children, 5 general practitioners and 3 association members were interviewed in May 2021. Anti-vaccination attitudes could be explained by: fear of serious adverse effects due to lackof information and knowledge, mistrust of scientists and pharmaceutical industry, importance of the relay by social networks. School, general practitioners, story-telling testimonials and chasing fame on television, played a central role to invert the balance and motivate children's vaccination.</p> <p>Interpretation</p> <p>Specificities of our population was fear for teenage pregnancy, which rate is high in Reunion Island. We should lift this taboo related to sexuality and encourage dialogue between children and their close social network. This better understanding of barriers and motivations will lead to solutions to expand this HPV vaccination promotion program across all Reunion Island.</p> <p>Funding</p> <p>The Reunion Regional Health Agency provided a grant.</p> |

## Background

In Reunion Island (a French overseas territory near the Eastern Coast of Madagascar in the Indian Ocean), uterine cervical cancer is the third most common cause of cancer in women and standardized mortality rate accounts for 4.8 for 100 000 women, three times higher than in France mainland<sup>1,2</sup>, yet human papillomavirus (HPV) vaccination coverage rate is low (12.2%)<sup>3</sup>.

Interventions that have proven their efficacy to strengthen vaccine coverage against HPV include : actions on knowledge (among children), actions on behavior (raising general practitioner awareness), actions on environment (offering free school based vaccination), and actions combining at least two strategies coming from different categories<sup>4</sup>. Thus during school year 2020-2021, we conducted a prospective, randomized controlled study in two middle school in Southern Reunion Island: PROM SSCOL<sup>5</sup>. In one intervention school we offered a health promotion program combining: students information during school classes, parents information by letter and phone calls, general practitioners information by letter and video conference call, free school-based vaccination (in a "health bus" parked in the schoolyard) with nonavalent HPV vaccine. This school was compared to a control school where no specific intervention was planned. We aimed at assessing the impact of this health promotion program on vaccination coverage.

Although this program significantly increased HPV vaccination coverage in the intervention school, participation rate was low, in spite of all our efforts to galvanize students (PROM SSCOL article, under review).

The main objective of the study was to understand the barriers and motivations to HPV vaccination in populations yet sensitized to its benefits. Findings solutions to remove these barriers would help us expand this promotion program across the whole Reunion Island.



## Methods

### *Setting*

The study was conducted among the population around the intervention school where the health promotion program was conducted during school year 2020-2021.

A qualitative study was adopted using a grounded theory approach to obtain an indepth understanding of issues pertaining to HPV vaccination.

### *Inclusion criteria*

Four investigators with two years of experience in qualitative research conducted interviews on the following populations:

- middle school students,
- parents of children randomly selected to participate to the study,
- school staff (teachers, director, nurse)
- general practitioners (GP) who practice in a perimeter of 5km around the middle school
- prevention coordinators working for an association, who animated prevention actions in the courtyard during vaccination campaigns.
- analyze of social networks content, facing television interviews of this vaccination campaign<sup>6-10</sup>

### *Data collection*

Semi-structured face-to-face and focus group discussions were conducted. After a short self-presentation, investigators asked respondents an icebreaker question and then probed with follow-up questions in an evolving interview process. A topic guide for interviews was developed based on a review of the existing literature and included considerations specific to the Reunion Island context. This topic guide was adapted over interviews.

Most of interviews took place inside the school (either in the health bus for intimacy, in a school class, or in the schoolyard). GP interviews were conducted in their office; parents were sometimes met in a coffee shop outside the school.

Interviews were audio recorded and transcribed verbatim. Field notes were made during and post interviews. Interviews were carried out until data sufficiency was reached. Sufficiency was confirmed by the absence of any new themes emerging during additional interviews.

### *Data analysis*

Data were analyzed following the methodology of grounded theory. Open and axial coding were used to identify emerging themes and to develop a definitive codebook. Two data coders independently coded the data for each population studied. The resulting codes were compared, and discrepancies were resolved by consensus. Interview data were triangulated. Data were modeled for each of the populations, and an overall model was generated for the entire studies populations.

The qualitative analysis method was implemented following the Consolidated Criteria for Reporting Qualitative research (COREQ)<sup>11</sup>.

### *Objectives*

The specific aims were (i) to explore the barriers to HPV vaccination in a population yet sensitized to its benefits; and (ii) to identify facilitators to administering HPV vaccine to adolescents in Reunion Island in order to expand this promotion program across the whole island.

### *Ethics*

- This research has received the favorable opinion of Independent Ethics Committee (IEC) of Ouest II of Angers (N° 20.05.14.35227 (2020/46)).

- This research was registered in the ANSM EUDRACT database under the n° 2020-002332-73

- This research was registered on the website <http://clinicaltrials.gov/> (ID: NCT04459221)

Authors obtained written and informed consent to participate in the study from participants and their parents (or holders of parental authority). Participants were guaranteed anonymity of data.

## Results

A total of 19 school staff members (mean age 41.4 years), 20 parents of middle school children (mean age 38.4 years), 39 children aged 11 to 16 years (23 interviewed individually and 16 in three focus groups), 5 general practitioners and 3 association members were interviewed in May 2021. Mean interview length was 23 minutes for staff members, 26 minutes for parents, 8 minutes for children, and 16 minutes for the others (Table 1).

An overall model of the data from interviews with the different populations is shown in Figure 1. Central barrier to HPV vaccination was vaccination fear, related to lack of information and knowledge. Written information did not appear appropriate in this population with high illiteracy rate who turned towards social networks to get answers. However, the latter gathered aggressive comments over HPV vaccination and conveyed fake news or insufficient or erroneous lay knowledge. Added to COVID pandemic and previous pharmaceutical scandals, this amplified fear, led to vaccine mistrust and negatively influenced vaccine decision. Teachers and school's aim was to instill critical thinking skills in order to invert the balance. General practitioners played a central role of reassurance. Moreover, personal or close family's experience and testimonies of HPV-induced disease participated to behavioral changes. The story-telling of one school staff member about his own HPV-induced throat cancer shocked students, and many came right afterwards to claim vaccination.

Unlike other vaccines, since HPV is a sexually transmitted infection, HPV vaccine was associated with sexuality that could result in teenage pregnancy, and was thus a taboo subject. In some families with low socioeconomical level, where priorities were focused on basic needs, such as eating to heart's content, projection into the future was weak and health prevention was subsidiary. These parents disinvested themselves from educational projects. Thus children were left alone to decide and have the last word since parental authority seemed to be overthrown. This widened the gap between parents and children, where interfamilial communication was already broken.

In other families, indecision was influenced by law ambivalence: since HPV vaccine was not compulsory, it may not be as important as other vaccines ; though parents were happy to have this choice of vaccinating or not. On the other hand, children feared to become infertile because of HPV vaccine, though when stimulated by the presence of journalists at school and for the fame of being on media coverage, they were very much likely to accept vaccination. PROM SSCOL seemed to positively impact HPV vaccine decision.

Participant quotes by theme are reported in Supplementary Table 1 and specific models for each population are presented in Supplementary Figures 1–3.

All the above-mentioned barriers were cited at different scales. Indeed, for children, pejorative vision of vaccination (including fear and lack of interest) was the major barrier, whereas for parents and school staff, main barrier was lack of information and knowledge, and for general practitioner, it was mistrust in scientists.

## Discussion

### Principal findings

Several combined factors explained anti-vaccination attitudes: the fear of serious adverse effects due to lack of information and knowledge, mistrust of scientists and pharmaceutical industry, the importance of the relay by social networks<sup>12</sup>. School, general practitioners, storytelling testimonials and chasing fame on television, played a central role to invert the balance and motivate children's vaccination.

### Comparison to previous work

Vaccine hesitancy has been described previously<sup>13,14</sup>, especially in Reunion Island<sup>15</sup>. Major barrier for children, was the pejorative vision of vaccination, including fear of needles<sup>16</sup> and fear of HPV vaccine as a whole. Indeed in this era with decreased trust in healthcare institutions tainted by pharmaceutical scandals<sup>17</sup>, growing technology and dominant place of social media, fake news take the lead<sup>18-22</sup>. Lay knowledge reveals a deep lack of information among children though also among parents<sup>13</sup> and could be a cause of this lack of interest<sup>23</sup>. This hesitancy was largely influenced by the particular weight of the anti-vaccine leagues in Reunion Island, in 2008-2010, led by Dr Philippe de Chazournes, which casted a negative halo around the subject<sup>24,25</sup>. However, it seems that nowadays, general practitioners in whom children and their parents trust, tend to reassure and encourage HPV vaccination.

Law ambivalence has been reported previously for other vaccine types, such as influenza and COVID-19<sup>26-28</sup>. Making vaccine mandatory would be an intrusion of the fundamental freedom of free and informed consent that population would reject<sup>12</sup>, though not constraining it corresponded to State disengagement towards the most disadvantaged for whom high price would be an additional barrier. Healthcare workers believed that the main motivation to vaccinate against influenza would be its mandatory character<sup>27</sup>; other investigations have shown very low levels of support for mandatory vaccination against COVID-19<sup>29,30</sup>. Participants

who reported to have a low or medium education had more chances to agree in making COVID-19 vaccines mandatory for everyone than participants with a high educational status<sup>28</sup>. One specificity of HPV vaccination was its relationship with sexually transmitted disease, and sexuality in general, which was a taboo in most families. A previous study observed that 59% of children have never addressed sexuality topic with their mother and 80% with their father<sup>31</sup>. Indeed sexuality was associated with pregnancy and although feared, adolescent pregnancy in Reunion Island is a reality since it represents 5% of all live births on the island<sup>32,33</sup>, which is seven times more frequent than in mainland France. When parents feared that vaccinating their children against HPV may encourage them to have sexual intercourse<sup>34,35</sup>, children dreaded infertility induced by HPV vaccine albeit recent studies demonstrate that HPV vaccine could rather prevent infertility<sup>36,37</sup>.

On the opposite, presence of journalists was a real motivation for HPV vaccination, in teenagers' chase for fame. Described reasons were children's search for acknowledgment and growing narcissism after familial abandonment<sup>38</sup>, especially among these children from underprivileged backgrounds ; and dreams of success, which could rise them in social class. We could use this media thirst of recognition to meet our needs and rise vaccine coverage. Investigating different population raised an issue: viewpoint difference among school staff and parents. Teachers thought parents lacked confidence in educational system, and were responsible for children's academic failure, probably echoing their own school failure ; teachers reproached parents their lack of preoccupation concerning their children's disinterest and absenteeism<sup>39</sup>. On the contrary, parents showed great interest in school since it represented a mean of social promotion for their children<sup>40</sup>.

### Strengths and limitations

The strength of the study was the trusting relationship that we established with the children, by spending a week with them during each vaccination campaign (for each of three doses). Thus, children's interviews were contributive. The individual semi-directive interview format

(and focus group interviews for children) proved to be an appropriate methodological choice given the topic at hand. Interviews were conducted by four researchers, each focusing on one type of population, which made it possible to cover a wide range of stakeholders, to explore different angles and to generate a diverse set of data<sup>41</sup>. By combining their findings, the researchers were able to provide a global view of barriers and motivations to HPV vaccination in Reunionese middle schools. Investigators worked together for data triangulation, to limit subjectivity.

However, the study has some limitations. Firstly, during PROM SSCOL study, we only had a short time for students' information during school classes, and also very limited time during breaks (20 minutes per half a day) to vaccinate voluntary participants. Secondly concerning this qualitative research of barriers, a selection bias linked to participants' personal motivations resulted from the fact that recruitment was on a voluntary basis. Nevertheless, theoretical sampling and recourse to different recruitment methods made it possible to reach data sufficiency. Moreover, most interviews took place during a short time period (one week), during the third campaign of vaccination at the end of school year. Topic guide was adapted over interviews.

Moreover, conducting this study in the middle of COVID-19 vaccine controversies caused harm. Indeed, politicized media coverage surrounding COVID-19 vaccination created a confusion with HPV vaccine<sup>42</sup>. Moreover, assemblies being forbidden by the government because of the pandemic, information meetings were cancelled, and we did not have the opportunity to meet parents face-to-face and reassure them, or to meet general practitioners to convince them about the utmost importance of the vaccine.

#### Future directions

Better answering population's expectations, will help us overcome barriers to HPV vaccination in middle school and effectively expand school-based vaccination in the whole Reunion Island.

Main perspective was communication improvement. Since written information has not proved its efficacy, education through oral discussion should be encouraged, including testimonies and personalized messages<sup>43</sup>. Indeed, experience with COVID vaccine uptake<sup>44</sup> proved that targeted information during school class, containing prosocial and altruistic messages, raised children's awareness towards protection offered by HPV vaccine, not only as individual protection, but also as herd immunity. Yet knowledge was not sufficient to guarantee effective vaccination<sup>45</sup>. Discussion between children and their close social network should be encouraged:

- (i) friends, who may have experienced vaccination, and influence positively;
- (ii) parents, who should address the topic of sexuality without any taboo;
- (iii) general practitioners, who are the principal source of trustworthy information. Even though general practitioners tried to address questions and safety concerns, they should receive training in how to better interpret lay knowledge, adapt to representations and recommend HPV vaccine to parents via presumptive announcements<sup>46</sup>.
- (iv) teachers who are key stakeholders in the HPV vaccination behaviors of adolescents<sup>47</sup>, and school staff members, who could testify about their own experience of HPV induced diseases.

Moreover, discussion between parents and school staff should be reinstaured.

School is supposed to develop students' critical skills towards social networks through lessons of education to media and information<sup>48</sup>. Indeed, we need to have standing plans for addressing the inevitable safety scares that come at unpredictable times and from unpredictable sources<sup>37</sup>. Although source of fake news, social media should be used to serve our purpose as well, through a single spokesperson<sup>49</sup>.

Recently, WHO Strategic Advisory Group of Experts on Immunization (SAGE) evaluated the evidence that has been emerging over past years that single-dose schedules provided



comparable efficacy to the two or three-dose regimens<sup>50</sup>. These recommendations will enable more people to be vaccinated and thus preventing them from having cancers and all their consequences over the course of their lifetimes. Methods have been described to reduce children's anxiety and pain during vaccination<sup>51-53</sup>.

## **Conclusion**

Main barriers to HPV vaccination was fear, related to lack of information. These barriers have been described previously, but what was specific to our population was this law ambivalence, and fear for teenage pregnancy, which rate is high in Reunion Island. We should lift this taboo related to sexuality and encourage dialogue between children and their close social network. This better understanding will lead to solutions to expand this HPV vaccination promotion program across the whole Reunion Island.

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## Declaration of interests

PLT and MB received travel grants from IPSEN.

## Data sharing

|  |  |
|--|--|
| Will individual participant data be available (including data dictionaries)? | Yes  |
| What data in particular will be shared?                                      | All of the individual participant data collected during the trial, after de-identification   |
| What other documents will be available?                                      | Study protocol is already published.   |
| When will data be available (start and end dates)?                           | Immediately following publication; no end date   |
| With whom?   | Anyone who wishes to access the data   |
| For what types of analyses?  | Any purpose  |
| By what mechanism will data be made available?                               | Proposals should be directed to <a href="mailto:phuong.tran@chu-reunion.fr">phuong.tran@chu-reunion.fr</a> ; to gain access, data requestors will need to sign a data access agreement |

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Table 1. Population characteristics

|  |                                    | all population n= |                    |                |
|--|------------------------------------|-------------------|--------------------|----------------|
|  |                                    | parents n= 20     | school staff n= 19 | children n=23* |
| gender n(%)                                |                                    |                   |                    |                |
|  | female                             | 14 (70)           | 9 (47.4)           | 14 (60.9)      |
|  | male                               | 6 (30)            | 10 (52.6)          | 9 (39.1)       |
| mean age in years (min-max)                |                                    | 38.4 (31-47)      | 41.4 (25-56)       | 14.3 (11-16)   |
| grade n(%)                                 |                                    |                   |                    |                |
|  | 6th                                | NA                | NA                 | 5 (21.8)       |
|  | 7th                                |                   |                    | 4 (17.4)       |
|  | 8th                                |                   |                    | 7 (30.4)       |
|  | 9th                                |                   |                    | 7 (30.4)       |
| vaccinal status n(%)                       |                                    |                   |                    |                |
|  | vaccinated                         | NA                | NA                 | 4 (17.4)       |
|  | not vaccinated                     |                   |                    | 19 (82.6)      |
| socio economic status n (%)                |                                    |                   |                    |                |
|  | managers and liberal professionals | 2 (10)            | 1 (5.2)            | NA             |
|  | teachers                           | 0 (0)             | 5 (26.4)           |                |
|  | employees                          | 11 (55)           | 13(68.4)           |                |
|  | unemployed                         | 7 (35)            | 0 (0)              |                |
| mean interview length (mean $\pm$ sd, min) |                                    | 26.6 $\pm$ 7.4    | 23.3 $\pm$ 5.9     | 8.3 $\pm$ 3.2  |

\*23 individual interview

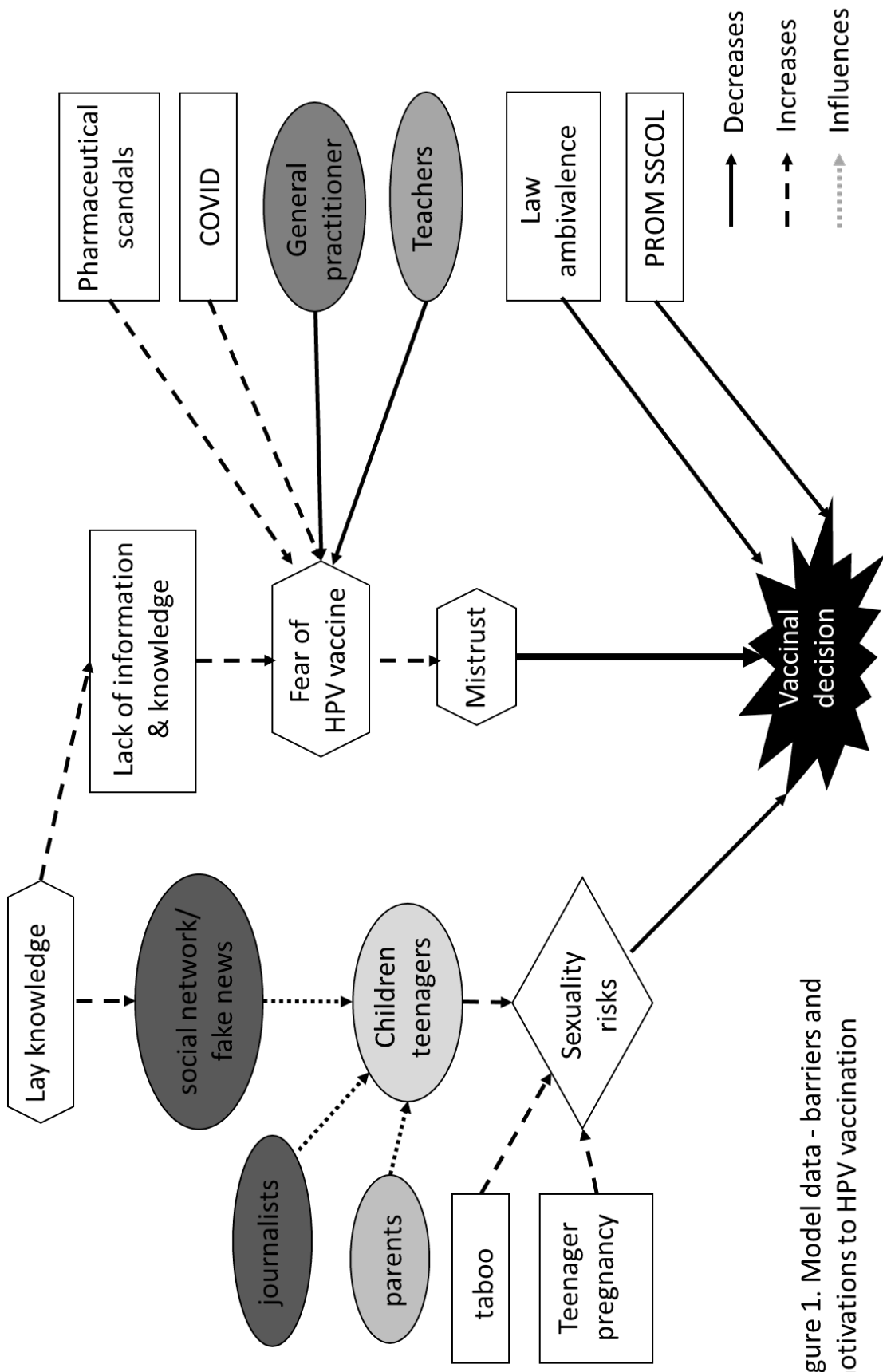


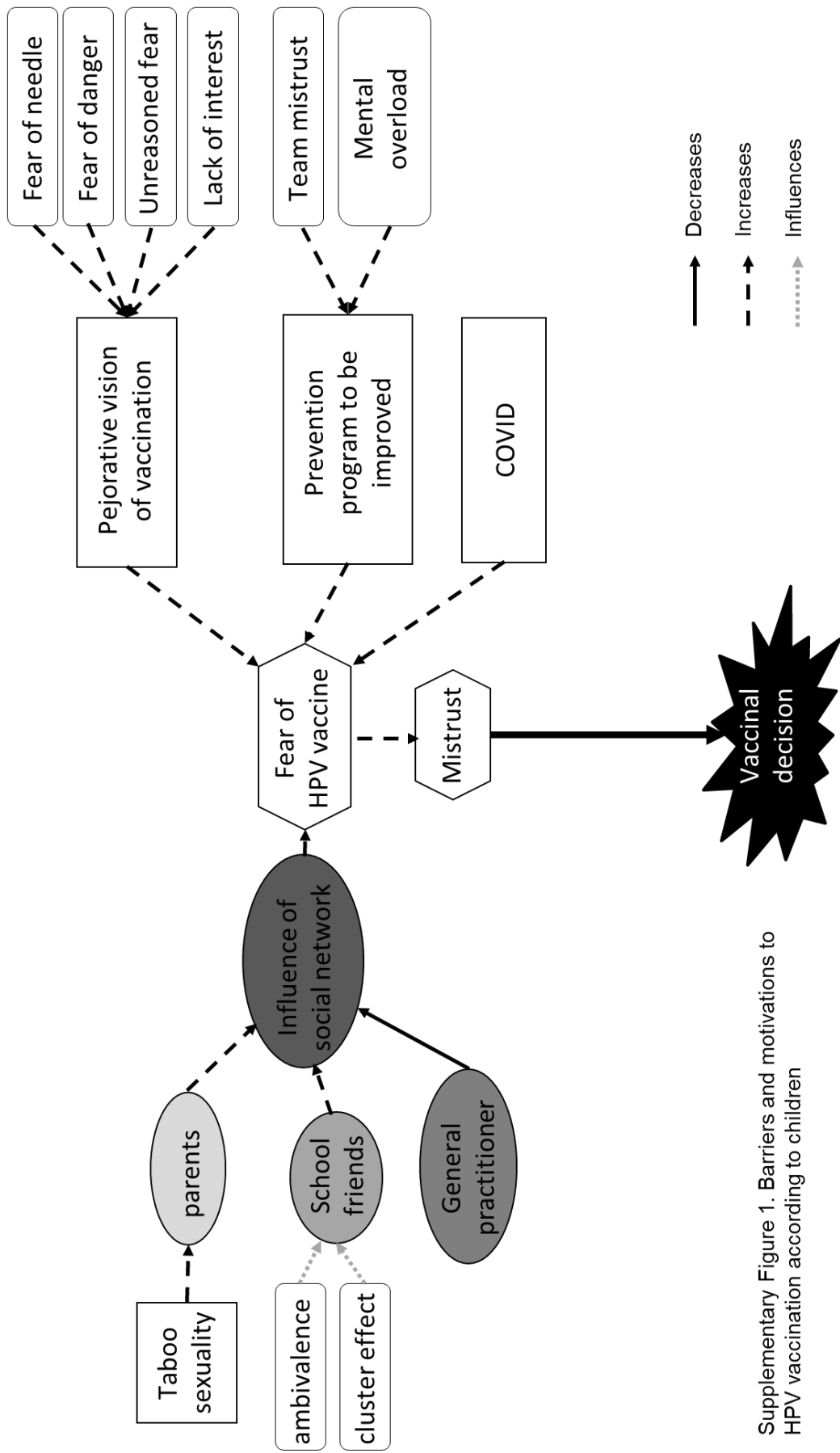
Figure 1. Model data - barriers and motivations to HPV vaccination



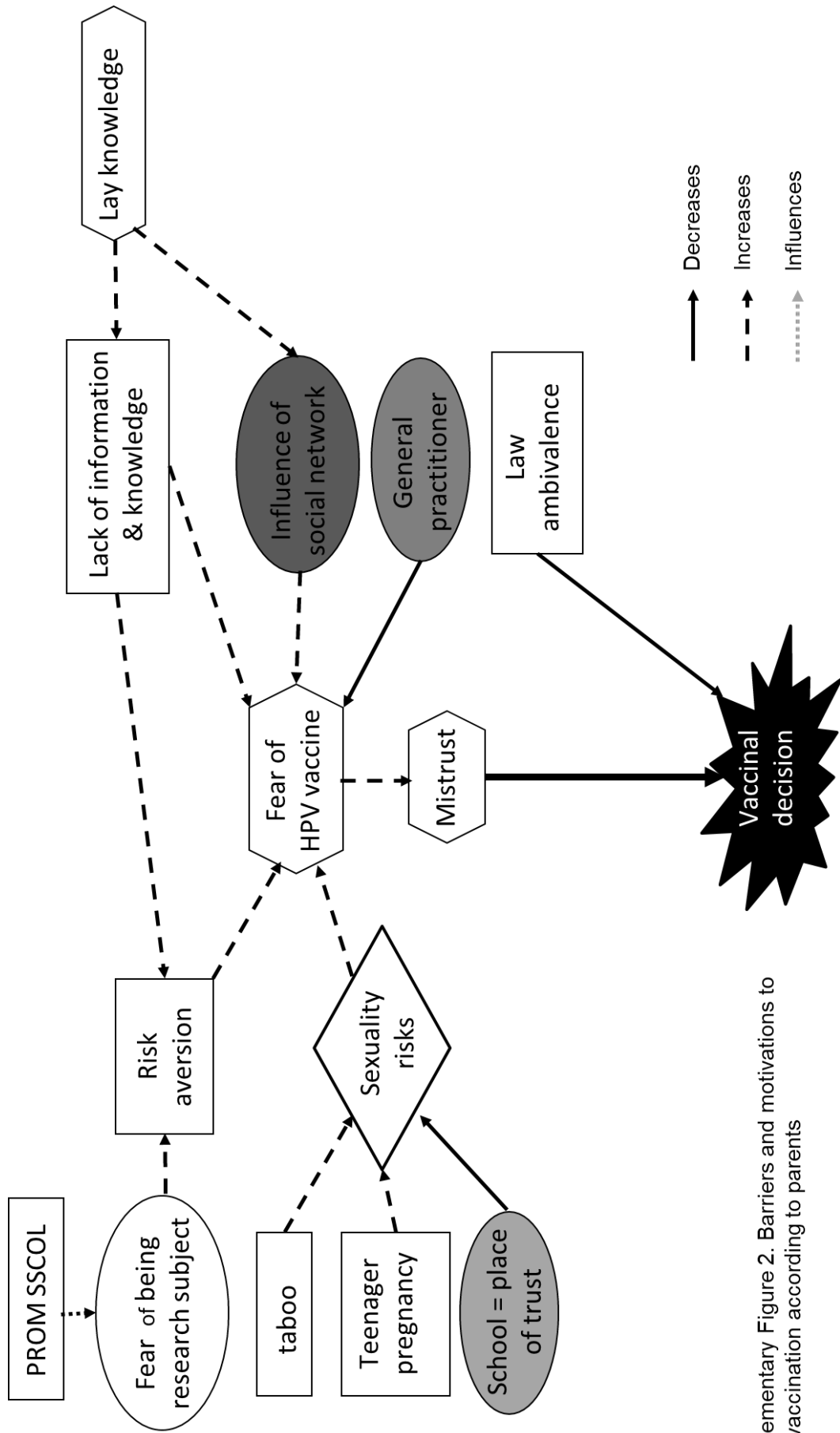
**Table S1. Verbatim examples from interviews with parents, school staff and children, Reunion Island**

| <b>Theme</b>                      | <b>Population<br/>(Number<br/>attributed to<br/>interviewees in<br/>chronological<br/>order of<br/>participation in<br/>the study)</b> | <b>Quotes</b>   |
|-----------------------------------|--|---|
| Lack of information               | Parent (1)   | "But I didn't even know this vaccine existed! I never heard about it before, my general practitioner never mentioned it!"   |
|                                   | Parent (9)   | "Even on TV they don't talk about this vaccine"   |
| Fear of HPV vaccine               | Child (5)  | "I don't know why I am scared, but I am scared."  |
|                                   | Child (9)  | "I wish my parents were there when I got vaccinated"  |
|                                   | Parent (3)   | "At work a colleague showed me a video of a child you became autistic after the vaccine"  |
|                                   | School staff (19)  | "One of my students asked me "Sir, can this vaccine make me ill?", I had heard about multiple sclerosis"  |
| Influence of general practitioner | Child (10)   | "I'll ask my general practitioner's opinion. If he tells me I have to do it, I'll do it, though I'd prefer him to vaccinate me rather than doing it in the bus"                             |
|                                   | School staff (16)  | "They had a doubt about the [HPV] vaccine, they talked with their general practitioner who advised them to do it"   |
|                                   | Parent (11)  | "I'll ask my general practitioner. He used to care for me when I was a child, and now he treats my daughter since she was born"   |
| Influence of parents              | Child (15)   | "My parents don't understand why it is important, they tell me this vaccine can kill me"  |
|                                   | Parent (8)   | "If this vaccine prevents my daughter from having children, how can I explain to her that all I wanted was to protect her? "  |
|                                   | Parent (15)  | "Times have changed, now teenagers have a say on their health, my daughter did not want to be vaccinated, she fears needles, I can't force her"   |
| Influence of social network       | Child (13)   | "I would be reassured to have others' opinion, this could make me change my mind"   |
|                                   | School staff (12)  | "Anybody can say anything now on the internet. Even people who know nothing can say their own truth"  |
| Pharmaceutical scandals           | Parent (20)  | "Why should we suddenly vaccinate our children against HPV ? Don't they earn enough money with COVID ?"   |
|                                   | Parent (17)  | "They [pharmaceutical industries] do this for money, they don't care about our children's health, I don't trust them"   |
| COVID 19                          | Parent (7)   | "With everything going on with COVID 19, I would rather like to wait before vaccinating my girl against HPV."   |
|                                   | School staff (13)  | "With this...; sanitary situation... we can't involve families, raise awareness, since we avoid mingling of people inside the school. This campaign does not arrive in the best conditions" |
|                                   | School staff (6)   | "With COVID 19, mistrust developed through media and social networks who relayed information about deaths following vaccination"  |

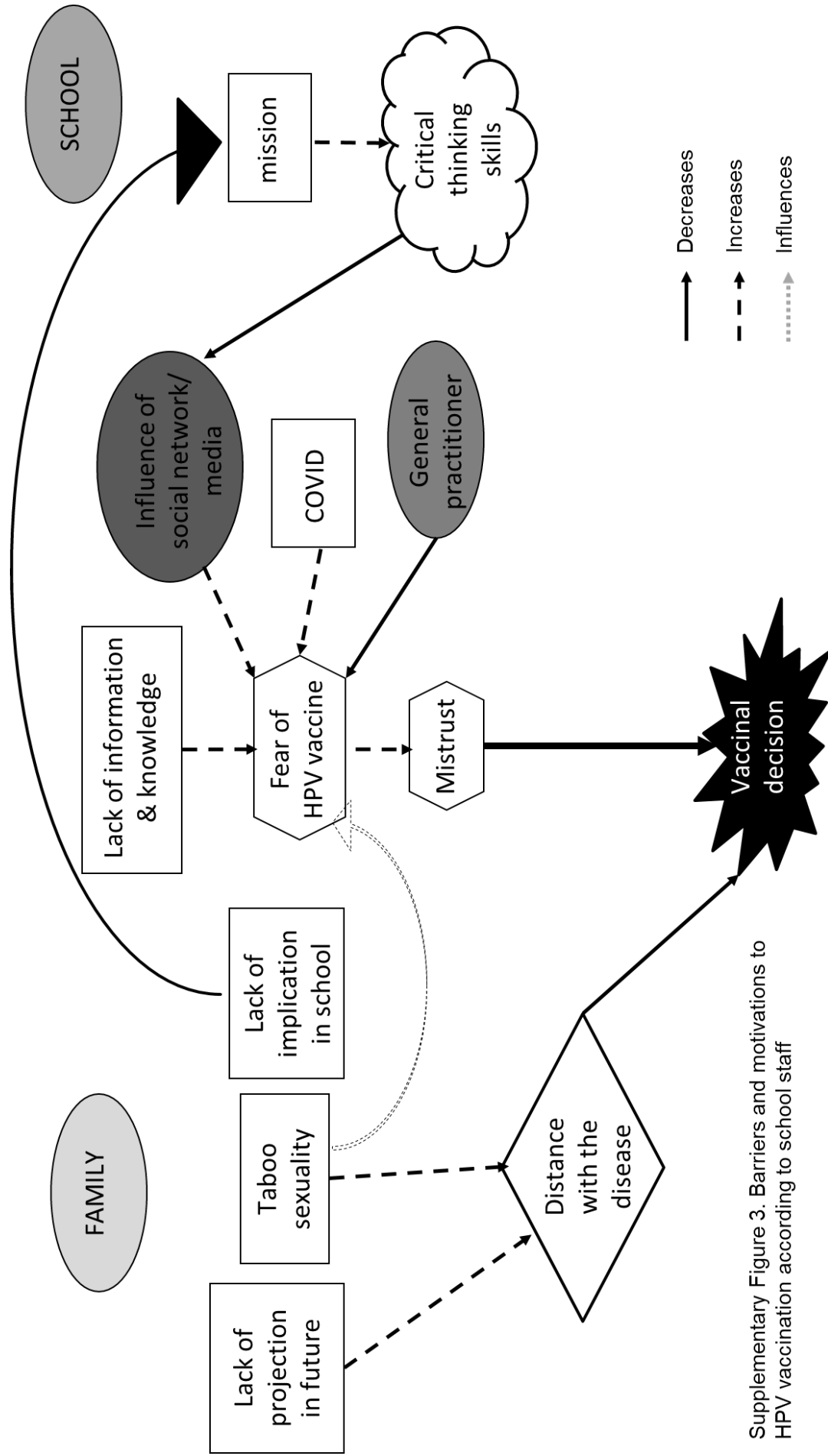
|                                  |             |  |
|----------------------------------|-------------|--|
| Law ambivalence                  | Parent (17) | “If this vaccine if not compulsory, it means diseases it is supposed to prevent, are not severe.”<br>“Look at tetanus, vaccine is compulsory because that disease will kill you if you catch it”   |
|                                  | Parent (6)  | “This vaccine is not compulsory, so I have the right not to vaccinate my son”  |
|                                  | Parent (16) | “If this vaccine becomes compulsory, I’ll do it, inevitably”   |
| Fear of being a research subject | Parent (14) | “Why did you choose my son’s middle school? If this vaccine is as important as you pretend, why not going into all middle schools?”  |
| Sexual taboo                     |             | “You get HPV if you have sexual intercourse. If you don’t have any sexual relation, vaccination is useless, because you can’t have HPV”  |
|                                  | Parent (14) | “Do you know how old is my daughter? Do you think she has ever had sexual intercourse?”  |
|                                  | Parent (9)  | This is way too young. Other children I don’t know, but my daughter is only a child.”  |
| Teenager pregnancy               | Parent (11) | “I don’t want my daughter to have early sexual intercourse. She is too young to be pregnant. You can’t put in their head that vaccine will protect them. Then they’ll have sexual intercourses without condoms and then if girls get pregnant at 15, what do we do?” |



Supplementary Figure 1. Barriers and motivations to HPV vaccination according to children



Supplementary Figure 2. Barriers and motivations to HPV vaccination according to parents



Supplementary Figure 3. Barriers and motivations to HPV vaccination according to school staff

**Article 6.** Moyens de communication pour aborder la vaccination HPV avec les adolescents

Résumé

Introduction. Au cours de l'année scolaire 2020-2021, nous avons mené une étude dans deux collèges du sud de l'île de La Réunion, où nous avons comparé le taux de vaccination HPV en fin d'année, suite à un programme de promotion de la santé. En parallèle, nous avons évalué trois stratégies de communication : une information ponctuelle des élèves pendant les cours (communication passive), une information tout au long de l'année scolaire avec une discussion personnalisée pendant les coloriages (communication opportuniste), et une information créée par les enfants eux-mêmes pour sensibiliser leurs camarades (communication participative).

Les objectifs de l'étude étaient d'évaluer l'impact de ces trois groupes recevant différents outils de communication sur l'acceptation théorique du vaccin contre le HPV, et la vaccination effective contre le HPV chez les adolescents.

Méthodes. La force de l'association entre le mode de communication et l'intention de vaccination ou le taux de vaccination effective a été mesurée en calculant les risques relatifs entre les groupes.

Résultats. Par rapport au groupe passif, le taux d'étudiants ayant l'intention de se faire vacciner contre le HPV était significativement plus élevé dans le groupe participatif (RR 2,6 [1,9-3,5],  $p < 0,001$ ) et dans le groupe opportuniste (RR 1,6 [1,2-2,0],  $p < 0,001$ ). De même, par rapport au groupe passif, la vaccination efficace est significativement plus performante dans le groupe participatif (RR 30,3 [8,9-103,0],  $p < 0,001$ ) et dans le groupe opportuniste (RR 12,9 [4,1-40,9],  $p < 0,001$ ).

Conclusion. La communication opportuniste et participative, y compris l'autonomisation pour la promotion de la santé des enfants et des adolescents, pourrait être une solution pour améliorer les connaissances des adolescents en matière de santé et, espérons-le, pour augmenter l'utilisation des vaccins.



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| <b>Title</b>       | Communication tools to address HPV vaccination with adolescents   |                      |
| <b>Abstract</b>    | <p>Introduction. During school year 2020-2021, we conducted a study in two middle schools in Southern Reunion Island, where we compared HPV vaccination rate at the end of the year, following a health promotion program. In parallel we evaluated three communication strategies: one-shot students information during classes (passive communication), information all along school year with personalized discussion during coloring artwork (opportunistic communication), and information created by children themselves to raise awareness among their peers (participative communication). The objectives of the study were to evaluate the impact of these three groups receiving different communication tools on theoretical HPV vaccine acceptance, and effective HPV vaccination among adolescents.</p> <p>Methods. The strength of the association between the communication mode and the vaccination intention or effective vaccination rate was measured by calculating the Relative Risks between the groups. Results. As compared with the passive group, rate of students with intention to vaccinate against HPV was significantly higher in the participative group (RR 2.6 [1.9–3.5], <math>p &lt; 0.001</math>) and in the opportunistic group (RR 1.6 [1.2–2.0], <math>p &lt; 0.001</math>). Similarly, comparatively to passive group, effective vaccination significantly outperformed in the participative group (RR 30.3 [8.9–103.0], <math>p &lt; 0.001</math>) and in the opportunistic group (RR 12.9 [4.1–40.9], <math>p &lt; 0.001</math>). Conclusion. Opportunistic and participatory communication, including empowerment for child and adolescent health promotion could be a solution to increase adolescents health literacy, and hopefully increase their vaccine uptake.</p> |                      |

## Communication tools to address HPV vaccination with adolescents

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## Introduction

In Reunion Island (a French overseas territory near the Eastern Coast of Madagascar in the Indian Ocean), uterine cervical cancer is the third most common cause of cancer in women and standardized mortality rate accounts for 4.8 for 100 000 women, three times higher than in France mainland (103). Cervical cancer results from human papillomavirus (HPV) infection. Primary prevention is based on HPV vaccination, which has proven to be effective in reducing the prevalence of HPV carriage, and the incidence of condyloma or intermediate grade cervical dysplasia (8,9), and invasive CC (104).

In France, HPV vaccination is recommended for adolescents (both girls and boys) aged 11 to 14 years (2 doses), with catch-up vaccination possible between 15 and 19 years of age (3 doses). In Reunion Island, coverage rate is the lowest in France (12.2%) (7).

One of the main barriers to HPV vaccination, is the lack of information (105,106), especially from teenagers. Thus, communication is of utmost importance to improve their knowledge about HPV diseases and to facilitate positive attitudes towards vaccination.

Content of this communication has been evaluated (107) : statements on vaccine safety and social conformism had the greatest potential to obtain highest vaccine acceptance. Nonetheless, there is little research on which format is most effective in educating adolescents (108), thus different communication formats are yet to be built.

During school year 2020-2021, we conducted a study in two middle schools in

Southern Reunion Island, where we compared HPV vaccination rate at the end of the year, following a health promotion program. In parallel we evaluated three communication strategies: one-shot students information during classes (passive communication), information all along school year with personalized discussion during coloring artwork (opportunistic communication), and information created by children themselves to raise awareness among their peers (participative communication).

The main objective of the study was to evaluate the impact of these three different communication tools on theoretical HPV vaccine acceptance among adolescents.

## **Material and methods**

### ***Setting and study design***

Full protocol of our prospective, controlled intervention study of superiority, is available(109). In each middle schools, we randomly selected three classes in each grade level (6<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup> and 9<sup>th</sup> grade).

In the control school, we offered students information during school classes at the end of the year (passive communication). A questionnaire (Supplementary material 1) was distributed to students at the end of the year, to evaluate their intention to vaccinate against HPV.

In the intervention school, a health promotion program was conducted during 2020-2021 academic year combining: students information during school classes, parents information by letter and phone calls, general practitioners information by letter and video conference call, free school-based vaccination (in a "health bus") with nonavalent HPV vaccine. A team of physicians (senior and junior) and association

members assisted the three vaccination campaigns (for each vaccine dose), offering vaccination itself, but also discussion with personalized information during school breaks, during coloring workshop with students who volunteered (opportunistic information).

One class from the intervention school was designated, upon teacher's motivation, to become health ambassadors and create a health empowerment campaign (participative communication). They named it "My health, my power", for prevention and screening of cancers. They developed competences such as : realization of a project, commitment making, initiative taking, identification of rules of individual and collective responsibility in health, oral presentation. All along school year, awareness raised among students about the importance of healthcare and the transmission of this message. They designed a poster with anti-cancer slogans that will be printed and displayed in all general practitioners' offices in Reunion Island. They presented their work in an assembly gathering 60 people, including other students, parents, teachers and local media (radio and television).

Main objective was to compare HPV vaccine acceptance between these populations. Secondary objective was to compare effective HPV vaccination.

### ***Data collection***

Questionnaires were distributed at the end of school year, to be filled by students at the end of information sessions, and were collected right afterwards.

### ***Statistical analysis***

Qualitative variables were expressed as numbers and percentages with their 95% confidence interval, quantitative variables as mean with their standard deviation (SD).

For qualitative data, intervention and control groups were compared by the Chi2 test or Fisher's exact test according to validity conditions. Hypotheses were tested with an alpha risk of 0.05, and confidence intervals were calculated at 95%. The strength of the association between the communication mode and the vaccination intention or effective vaccination rate was measured by calculating the Relative Risks in the two groups "opportunistic communication" and "participative communication" compared to the group "passive communication". All statistical analyses were performed using STATA SE V16® software (StataCorp, Texas).

### ***Ethics***

This research has received the favorable opinion of the Committee for the Protection of Persons of Ouest II of Angers (N° 20.05.14.35227 (2020/46)). Authors obtained written and informed consent to participate in the study from participants and their parents (or holders of parental authority).

### ***Role of the funding source***

The funding body did not play any role in the design of the study, collection, analysis, interpretation of data, or writing the manuscript.

## **Results**

### *1/ Passive communication (Figure 1)*

In the control school, students information concerned 259 students. We managed to retrieve 78% (202/259) fulfilled questionnaires, among 104 boys and 98 girls, with a

mean age of  $12.6 \pm 2.4$  years. To the question “If a health bus was to come to your school, would you like to benefit from HPV vaccination at school?”, **acceptance rate was 31.1%** (63/202). Main reasons for refusal was “fear of parents’ disagreement” (25.2% of students thought that their parents were against HPV vaccination) or “fear of the needle” (23.6%). Most of students (71.8%) did not know their vaccinal status concerning HPV, though knowledge rate was similar concerning their other vaccines. Nine students declared that they were vaccinated against HPV, although evidence from health record only highlighted **1.5%** (3/202) **of effective HPV vaccination**.

## *2/ Opportunistic communication (Figure 2)*

In the intervention school, classes randomly selected concerned 245 students, of whom 61.6% (151/245) answered the questionnaire. It was difficult to quantify the number of children participating to coloring workshop, since they were coming in groups, some children belonging to the classes randomly selected in the health program, others not. Some students came several times, and length of stay was variable. Objective **acceptance rate for HPV vaccination** in questionnaires **was 48.3%** (73/151). Yet **vaccination**, whether it be in the health bus or not, was **effective in only 19.2%** (47/245) of the students in this intervention school by the end of school year.

In questionnaires, 11.9% (18/151) pretended they were vaccinated against HPV whereas health records denied vaccination for two students; 26.5% (40/151) said they were not vaccinated whereas 35% (14/40) of them benefited from vaccination in the health bus in the school and 61.6% (93/151) did not know their vaccinal status whereas 24.7% (23/93) were vaccinated – 20 in the health bus, and three with their general

practitioner.

### *3/ Participative communication (Figure 3)*

One class in 9<sup>th</sup> grade, with 20 students aged between 14 and 15 years old, created a health empowerment campaign, with slogans in creole language (dialect in Reunion Island). They met 6 times with their main teacher and a member of the coordination center of cancer screening. An anonymous survey was conducted at the end of the project to evaluate students' feeling all along school year (Table 1). All students filled it though 30% (6/20), did not answer most of the question. Half the class was happy to participate to this project, and majority (60%) found it useful. **Acceptance rate** of the broadcasted messaged, including **HPV vaccination was 80% (16/20)**. None of these students brought their health record ; though **upon declaration, 45% (9/20) claimed to be vaccinated**. Students listening to the oral presentation in the assembly, seemed enthusiastic, though no evaluation of the intention to vaccinate among that population of peers was realized.

As compared with the passive group, rate of students with intention to vaccinate against HPV was significantly higher in the participative group (RR 2.6 [1.9–3.5],  $p < 0.001$ ) and in the opportunistic group (RR 1.6 [1.2–2.0],  $p < 0.001$ ). Similarly, comparatively to passive group, effective vaccination significantly outperformed in the participative group (RR 30.3 [8.9–103.0],  $p < 0.001$ ) and in the opportunistic group (RR 12.9 [4.1–40.9],  $p < 0.001$ ).

## **Discussion**

Communication including participation to a health program, seemed the best way to involve adolescents and increase their HPV vaccine acceptance, rather than didactic presentations. Opportunistic communication is another possible approach to target adolescents.

Art therapy has been described in psychiatry (110) to incite patients to confide, in a healing process. However, to our knowledge, no experience of art or coloring workshop has been described as such as a mean of getting a message across.

In general, interventions to increase vaccine uptake perform better when they include multicomponent communication strategies and/or have a focus on dialogue-based approaches (111). However dialogue can be particularly challenging for parents because it involves discussing how HPV is sexually transmitted. School comes to support development of students' critical skills (112). Indeed adolescents at that age, are developmentally positioned to begin making informed decisions about their health and well-being (111).

Health promotion programs including empowerment for child and adolescent health promotion are emerging over the past years (113), with a variable relationship between children and adults. All these health programs aim to increase adolescent health literacy (114), by providing age-appropriate information regarding benefits of HPV vaccination and actively include adolescents' view in vaccination decision.

With growing social networking, adolescents can easily spread their negative



perceptions about vaccinations (115,116). However, their sharing of positive attitudes towards vaccination is poorly described. In this study, we described one format of empowerment campaign, offering adolescents in the participative group: the possibility to present their enthusiasm and poster they designed, among an assembly of peers.

Another form of participatory design approach was serious videogame, which was proven effective to engage different health behaviors and to promote HPV vaccination communication and uptake (111,117–120). Indeed it promoted learning through exploration, experimentation and empowerment; and fostered conversation with parents.

### ***Strengths and limitations***

To our knowledge, this is the first study to build communication tools such as coloring workshops to disseminate opportunistic information; or such as empowerment campaign with adolescents' participation.

In the opportunistic group, acceptance rate of HPV vaccination in that population was 48.3% though when asking students individually at the end of each coloring session, this rate seemed higher, though difficult to quantify. Nonetheless, it was difficult to evaluate which part led to a higher acceptance rate: was it the presence of the school bus in the school courtyard three times during the year, with repetitive information? Or was it this possibility of having free speech while coloring? Neither was it possible to evaluate the impact of their empowerment campaign upon their peers.

One limitation was the low participation rate in questionnaires. In the participative group, even though the majority seemed happy to participate to the project, one third of the class did not answer most of the questions: was it a lack of interest? Thus 80%-acceptance rate in this population may be overestimated. Moreover, since effective

vaccination in that group was not checked upon health record, their self-report of vaccination may also be magnified.

Indeed, in the opportunistic group, we noted a discordance between intention to vaccinate and effective vaccination. Although intent to undergo HPV vaccination was significantly associated with HPV vaccine uptake, this difference between intent and uptake has been underlined before (121). A qualitative study evaluating barriers to HPV vaccination in this population, is in process (personal data).

In conclusion, strategies are urgently needed to increase the uptake of HPV vaccination among preteens. One of the strategic objectives of Global Vaccine Action Plan, is that “individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility”. Opportunistic and participatory communication, including empowerment for child and adolescent health promotion could be a solution to increase adolescents health literacy, and hopefully increase their vaccine uptake.

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## **Declaration of interests**

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Table 1. Survey in the participative group

|  |  | Student, n=20 |
|--|--|---------------|
|  |  | n (%)         |
| 1. How did you feel about this campaign?                   |  |               |
|  | not happy at all                         | 1 (5)         |
|  | not happy                                | 2 (10)        |
|  | mixed                                    | 7 (35)        |
|  | happy                                    | 9 (45)        |
|  | very happy                               | 1 (5)         |
| 2. Do you find this campaign useful for you?               |  |               |
|  | Yes                                      | 12 (60)       |
|  | No                                       | 2 (10)        |
|  | No answer                                | 6 (30)        |
| 3. Did you find this project difficult?                    |  |               |
|  | Yes                                      | 1 (5)         |
|  | No                                       | 13 (65)       |
|  | No answer                                | 6 (30)        |
| 4. Do you think you could use this campaign in the future? |  |               |
|  | Yes                                      | 12 (60)       |
|  | No                                       | 2 (10)        |
|  | No answer                                | 6 (30)        |
| 4'. How could you use this project?                        |  |               |
|  | Talk around about it                     | 7 (35)        |
|  | Use the acquired knowledge               | 1 (5)         |
|  | Think about consequences of our actions  | 1 (5)         |
|  | No answer                                | 11 (55)       |
| 5. Which competences do you think you acquired?            |  |               |
|  | Oral fluency                             | 8 (40)        |
|  | Information                              | 1 (5)         |
|  | Knowledge about cancer                   | 1 (5)         |
|  | Confidence                               | 1 (5)         |
|  | None                                     | 1 (5)         |
|  | Being bored                              | 1 (5)         |
|  | no opinion                               | 7 (35)        |
| 6. Which part did you prefer?                              |  |               |
|  | First (sharing information about cancer) | 5 (25)        |
|  | Middle (preparation and repetitions)     | 5 (25)        |
|  | Last (oral presentation)                 | 3 (15)        |
|  | No answer                                | 7 (35)        |
| 7. Do you feel like a health ambassador?                   |  |               |
|  | Yes                                      | 9 (45)        |
|  | No                                       | 5 (25)        |
|  | No answer                                | 6 (30)        |



Figure 1. Passive communication, information during school classes

This information session was conducted during school year 2020-2021 during COVID pandemic, obliging us to wear face masks.



Figure 2. Insidious communication, coloring workshop

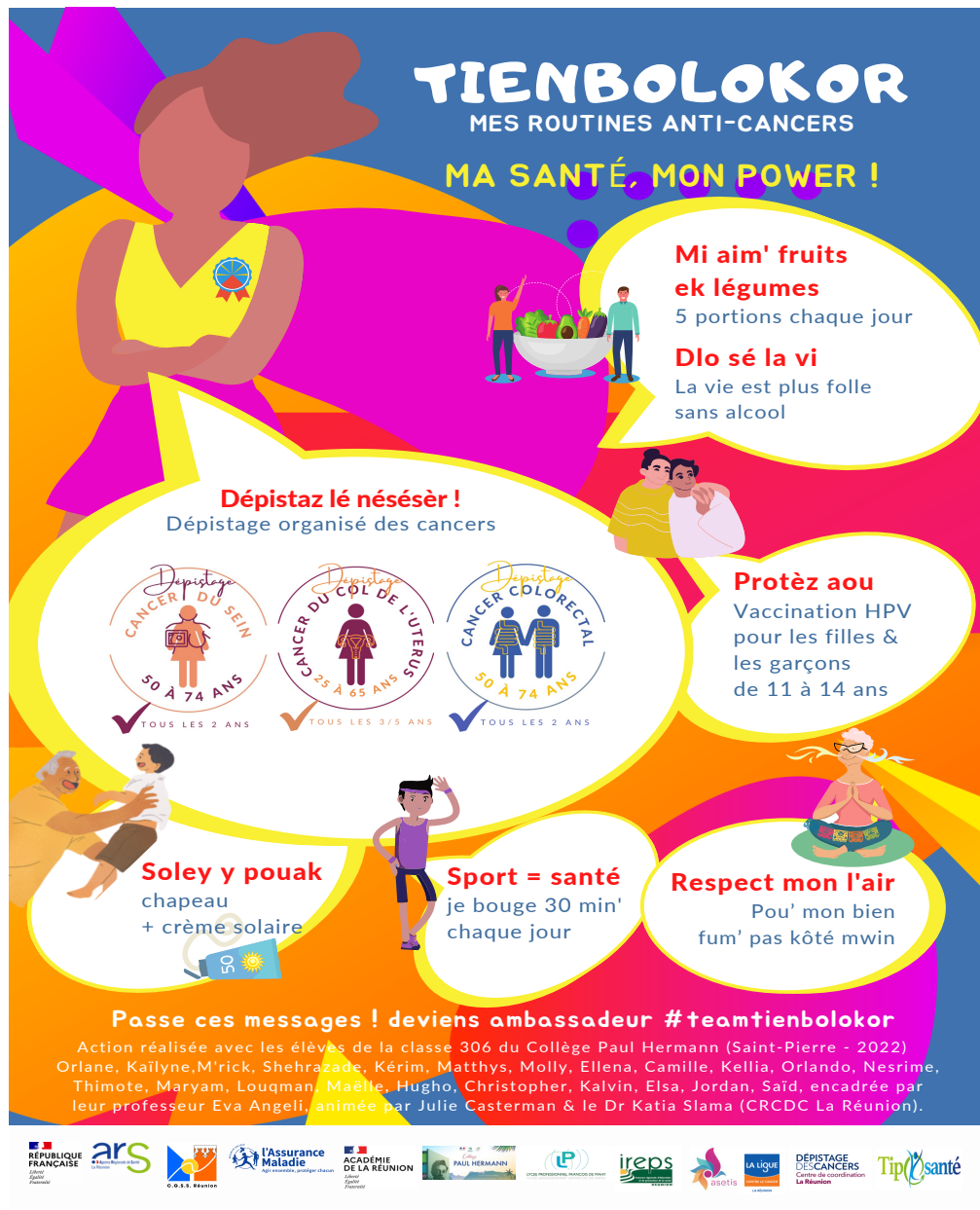


Figure 3. Participative communication, creation of prevention poster

“My anti-cancer routine. My health, my power.  
I like fruits and vegetables – 5 portions each day  
Water is life – life is crazier without alcohol  
Screening is necessary – breast cancer: 50-74 years, every 2 years ; cervical cancer 25-65 years old, every 3-5 years ; colorectal cancer : 50-74 years, every 2 years  
Protect yourself : HPV vaccination for girls and boys 11-14 years old  
Sun can burn – hat + sun cream  
Sport = health – I move 30minutes every day  
Respect my air – don’t smoke next to me”



## IV. DISCUSSION

### A. RESULTATS PRINCIPAUX

A La Réunion, malgré la prévalence élevée des HPV 16, 31, 51, 52, pour la plupart contenus dans le vaccin Gardasil 9, le taux de couverture vaccinale contre le HPV est faible (12,2%). Les principaux freins étaient le manque d'information et une méfiance envers les vaccins. Notre étude pilote menée auprès de deux collèges dans le sud de l'île, a montré qu'un programme de promotion de la santé sexuelle et de la vaccination HPV, permettait d'augmenter significativement le taux de vaccination. Le mode de communication le plus efficace pour augmenter l'acceptabilité de la vaccination parmi les élèves, était la méthode participative, où les élèves étaient acteurs dans la création d'une campagne de santé publique. Cependant le faible taux de participation aux campagnes vaccinales pouvait être expliqué par la crainte d'effets indésirables graves par manque d'information et de connaissances, la méfiance, et le tabou lié à la sexualité et aux grossesses chez les mineures, privant les enfants d'un dialogue avec leurs parents sur le sujet.

### B. PERSPECTIVES D'AVENIR

Sur l'île de La Réunion, il existe une faible prévalence du HPV 18, mais une répartition différente des infections à HPV. Cependant le nombre d'échantillons exploitables était faible, et l'étude remonte à 2012. Au vu de la mixité de la population à La Réunion, il serait intéressant de refaire le point sur les génotypes de HPV circulants actuellement sur l'île de La Réunion.

Bien que nous ayons montré une augmentation significative du taux de vaccination HPV après des actions de promotion de la santé sexuelle en collège, ce taux (19,2%) était insuffisant au vu de l'énergie déployée et des moyens mis en œuvre. Pour pouvoir étendre ce dispositif à l'ensemble de l'île de La Réunion, il va falloir optimiser les actions de santé.

Un projet similaire (PrevHPV) a été mis en place dans plusieurs villes en France métropolitaine (24). Dans leur phase diagnostique, ils ont évalué comment optimiser la communication avec les adolescents, notamment, sur le contenu à privilégier pour améliorer leurs connaissances et faciliter leurs attitudes positives. Ils ont aussi co-

construit des formats et des contenus pour usage en classe, avec supports d'enseignement, vidéo, jeu sérieux. Après quelques échanges avec certains membres de ce projet, l'idée serait un partage de connaissance et des outils pédagogiques à diffuser aux adolescents.

Le manque d'information concerne aussi la population générale, mais aussi certains médecins généralistes encore campés sur leur position anti vaccin. Avant de mettre en place un programme généralisé sur l'île, il faudra une phase préparatoire de diffusion massive et de vulgarisation de l'information pour que tous comprennent l'enjeu de la vaccination anti HPV.

En parallèle à cette amélioration de la prévention primaire, il faudra mener des actions d'optimisation du dépistage contre le cancer du col de l'utérus, de la surveillance des lésions précancéreuses et de prévention des récives de cancer ou de lésions précancéreuses après traitement. Plusieurs études sont actuellement en cours pour évaluer ces différents points.

## V. CONCLUSION

Dans ce travail, nous avons mis en évidence qu'un programme de promotion de la santé sexuelle alliant information des adolescents et de tout leur réseau (parents, médecins généralistes, professeurs), et une vaccination au sein même du collège, permet d'augmenter significativement la couverture vaccinale contre le HPV.

Nous avons été confrontés à de nombreux défis : faible taux de participation malgré de nombreuses relances, difficulté de communication auprès des adolescents, mais aussi de leurs parents, avec de nombreux consentements à signer dans cette population avec un taux élevé d'illettrisme, la mésinformation concernant le vaccin anti HPV, le covid etc.

L'analyse des freins et des motivations à cette vaccination anti HPV en collège, ainsi que l'évaluation de différentes pistes pour communiquer avec les adolescents, vont nous permettre d'améliorer et optimiser ce dispositif, pour l'étendre à l'ensemble des collèges de l'île de la Réunion, prévu normalement pour la rentrée scolaire 2024. On espère ainsi augmenter la couverture vaccinale contre le HPV à La Réunion, qui reste un des plus faibles au monde.

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