**Title page**

# Effect of Internet use for searching information on vaccination on the uptake of human papillomavirus vaccine in France: a path-analysis approach

Fadia Dib[1,2], Philippe Mayaud[3], Laetitia Longfier[4], Pierre Chauvin[2], Odile Launay[1,5]

[1] INSERM CIC 1417, F-CRIN, I REIVAC; Assistance Publique- Hôpitaux de Paris, Hôpital Cochin, Paris, France
[2] INSERM, Sorbonne Université, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France
[3] London School of Hygiene and Tropical Medicine, London, United Kingdom
[4] IDM Families, Issy-les-Moulineaux, France
[5] Université de Paris, Faculté de médecine Paris Descartes, Paris, France

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**Corresponding author**

Dr Fadia Dib
Institut Pierre Louis d'Epidémiologie et Santé Publique
UMRS 1136 - 27 rue de Chaligny - 75012 Paris, France
Fadia.dib@inserm.fr

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# Abstract

Internet is a popular source of information regarding vaccination. This study aimed to determine whether there is a negative association between Internet use among French vaccine-hesitant mothers and HPV vaccine uptake by their daughters, and to gain insight into the pathways that would link Internet use to the lack of HPV vaccine uptake. We conducted a pooled cross-sectional analysis across the 2015, 2016, 2017 and 2018 Vaccinoscopie® Survey. Multivariate logistic regression and path models were used in the analysis. The study sample included a total of 2038 respondent mothers. Of those, 89 (4.4%) declared having never been in the situation of searching for information regarding a vaccination they had hesitated about, leaving 1949 mothers for the present analysis. Approximately 24% (466/1949) of the mothers declared using the Internet as a source of vaccine information. In multivariate logistic regression adjusted for physician recommendation of HPV vaccination, attitudes towards vaccines in general, perception of HPV vaccine usefulness, maternal level of education, region of residence, and the survey year, the use of Internet by the mothers was significantly associated with a lower HPV vaccination among their daughters (adjusted odds ratio (aOR), 0.66; 95% confidence interval (CI), 0.47-0.91). Path analysis further confirmed the negative effect of Internet use ($\beta$ =-0.10, standard error (SE)=0.02, P<0.0001), highlighting how the Internet plays a detrimental role in HPV vaccine uptake through a lower perceived level of HPV vaccine usefulness, a lower perceived level of information on childhood vaccination, and unfavorable attitudes towards vaccination in general.

1 **Manuscript**

2 **INTRODUCTION**

3 Since its introduction in the French immunization program in 2007, the initiation rate of HPV

4 vaccination in girls aged 15 years only reached 29.4% at its highest point, in 2018 (1). The same

5 year, the coverage rate for a two-dose regimen among 16-year-olds girls was estimated at

6 23.7% (2). This figure represents less than half of the target set for a two-dose regimen (3). The

7 HPV vaccine appears among those viewed less favorably in 2016 in France (4), against the

8 general background of a noticeable rise in vaccine hesitancy (5), which may be viewed as pretty

9 astonishing in Pasteur's country.

10 Internet has become a popular source of information regarding health-related topics, and HPV

11 vaccine makes no exception. Indeed, this vaccination is a popular topic among "googling"

12 searches for vaccine-preventable infectious diseases (6). The Eurobarometer Survey on the

13 European citizens' digital health literacy conducted in 2014 showed that around one out of two

14 respondents in France have used the Internet to search for health-related information within

15 the last year, 40% of whom indicated looking on behalf of their children. The French National

16 Health Barometer Survey conducted the same year showed that as many as 69 % of the French

17 population used the Internet to search for health-related topics (7).

18 Whilst the Internet represents a remarkable tool for health information dissemination, it also

19 provides a medium where misinformation (misinformed advice) and disinformation (deliberate

20 falsehoods) (8) are easily introduced, accessed and spread. This has become more problematic

21 as we live in an era of "post-truth" (defined by Oxford dictionary as "circumstances in which

22 objective facts are less influential in shaping public opinion than appeals to emotion and

23 personal belief"(9)).  in  The use of social media (such as Facebook) and messaging platforms

24 (such as WhatsApp) allows instant global dissemination of false information (10). This comes

25 with its own share of challenges in the health information field. For example, one study

26 analyzing the reach of online disinformation in Europ(9)e showed that the most popular false

27  news website in France, a website claiming to "vulgarize information on health and wellness",

28  had received approximately as many interactions on social media (shares, comments, reactions)

29  as five prominent and reliable French news websites combined (11). The spread of

30  misinformation on the benefits and risks of vaccines has certainly been fueling vaccine hesitancy

31  (12)(13)(14)(15), although it remains to be seen to what extent this translates into the decision

32  to vaccinate. The World Health Organization has listed the "uncontrolled dissemination of

33  misinformation" - including in the field of vaccination - among its urgent health challenges for

34  the next decade (16).

35  HPV vaccination in France provides an interesting case study of challenges facing vaccination in

36  an era of online mis/disinformation, as the introduction of the HPV vaccine in the French

37  vaccine immunization program has coincided more or less with the rise of social media

38  utilization. Furthermore, HPV vaccination in France is delivered opportunistically through

39  healthcare providers, with no dedicated school-based vaccination program. Therefore, parents

40  who have not heard about the HPV vaccine from their healthcare providers may have questions

41  to be answered about this vaccination.

42  In this context, we aimed to determine whether there was a negative association between

43  Internet use among French vaccine-hesitant mothers and HPV vaccine uptake by their

44  daughters, and to gain insight into the pathways that would link Internet use to a lack of HPV

45  vaccine uptake. Such an understanding is required to fully appreciate the impact of the Internet

46  on the uptake of HPV vaccination in France, and provide relevant data for policymakers and

47  practitioners to take necessary action.

48  **METHODS**

49  **Data source**

50  This study was carried out using the data acquired from the 2015, 2016, 2017 and 2018

51  Vaccinoscopie® Survey modules targeting mothers of girls aged 14 and 15 years. The

52  methodology of this survey commissioned by GlaxoSmithKline (GSK) and conducted by IDM

53  Families, an independent market research and polling company, has been published in detail

4

54      elsewhere (17)(18). Briefly, Vaccinoscopie® is a pluriannual web-based survey among French

55      representative quota samples of mothers, with respect to the socio-professional category (SPC)

56      of the reference person in the household, the number of children, and the geographic region of

57      residence, per child's years of age. It has been designed to monitor the dynamics of childhood

58      vaccine coverage, and perception and attitudes towards vaccination in France. A new sample of

59      study participants is interrogated from one year to another.

60      **Study variables**

61      The dependent variable was HPV vaccine initiation (i.e., the receipt of at least one dose of HPV

62      vaccine) in the 14-15 year-old daughter. The exposure of interest was "Internet use by the

63      mother" (yes/no), given the mother's answers to the question "When you hesitate about a

64      vaccine, what source(s) of information do you turn to to decide whether or not to have your

65      child vaccinated?". This question had a multiple-choice response format. For the purpose of this

66      analysis, we derived a dummy variable for each source of information.

67      Guided by reviews of the literature on the factors associated with HPV vaccine uptake (19)

68      (20)(21), we took into account the following relevant factors in the association between the

69      exposure of interest and the dependent variable:  1) mother's demographics and socioeconomic

70      stratus: age, level of education, household income and geographical region of residence; 2)

71      maternal attitudes towards vaccination in general (response to the single answer question "How

72      do you feel about vaccines?": in favour of vaccinating against all serious diseases if there are

73      vaccines/ in favour of minimizing the number of vaccinations/ opposed to all vaccines/ no

74      opinion), and perception of HPV vaccine usefulness (response to the single answer question

75      "For each of these diseases (cervical cancer), supposing there was a vaccine, would vaccinating

76      your child seem: indispensable/ useful/ not very useful/ useless/ do not know"); 3) physician

77      recommendation of HPV vaccination (response to the single answer question "Has your doctor

78      advised you to have your child vaccinated against HPV": yes/ no/ do not remember); 4)

79      perceived level of information regarding childhood vaccination (response to the single answer

80      question: "Do you think you are well informed about child vaccinations?": not at all well-

81      informed/ rather not well-informed/ rather well-informed/ fully informed and); and 5)

82  daughter's usual medical follow-up setting (response to the single answer question : "Your child

83  is followed by : a general practice/ a pediatrician practice/ a free preventive clinic for mother

84  and infants").

## Statistical analysis

86  We conducted a pooled cross-sectional analysis across the four aforementioned years of the

87  Vaccinoscopie® Survey. We combined these data sets in order to achieve a large enough sample

88  size to perform multivariate analysis. The data sets included data weighted according to the

89  French general population census of the French National Institute for Statistics and Economic

90  Studies. Although the data were generated each year from a quota sample and not from a

91  random probability one, we decided to conduct inferential statistical analysis commonly used to

92  make inferences about the larger population from which the sample was drawn. Since it is

93  difficult to guarantee that the study sample is representative for characteristics other than

94  those for which quotas units have been set,  inferential statistical measures (95% confidence

95  intervals (95%CI) and P-values) are meant only for indicative purposes in the present study.

96  *Logistic regression analysis*

97  We conducted a descriptive analysis of study variables followed by a bivariate analysis, where

98  HPV vaccine initiation was regressed on the covariates, which were were assessed for

99  multicollinearity beforehand. We then estimated a multivariate logistic regression model using a

100  backward selection process, with a threshold of P=0.20 for a variable to stay in the model. The

101  full model included the year of the Vaccinoscopie® Survey, in addition to the aforementioned

102  exposure variable and covariates. For ease of interpretation, we used the grouping of response

103  modalities required by the path analysis described below. The goodness-of-fit of the final model

104  was tested using the information matrix test.

105  Crude and adjusted odds ratios were calculated with their 95%CI.

106  *Path analysis*

107  We formulated a general hypothetical model for how Internet use, attitudes towards childhood

108  vaccination, perceived usefulness of HPV vaccine, and the other above mentioned factors might

109  be interrelated to HPV vaccine uptake. The hypothesized interrelationships between the

110    variables are depicted in a conceptual model in **Figure 1.** To test our proposed hypothetical

111    model, we applied path analysis, a form of statistical modeling consisting of a set of linear

112    equations that simultaneously assess the relationships between the measured variables. We

113    conducted these analyses using the PROC CALIS procedure in SAS with the weighted least

114    squares (WLS) estimation method, which handles categorical variables (22). Nominal variables

115    with more than two categories of response modalities (geographic area of residence, perceived

116    usefulness of HPV vaccine, attitudes towards childhood vaccination, and perceived level of

117    information) were dichotomized by grouping responses modalities, as the PROC CALIS

118    procedure handles continuous, binary and ordinal variables, but not nominal variables.

119    We first tested the hypothesized conceptual model, which included all possible associations

120    between variables **(Figure 1).** Afterward, we reviewed the path coefficients to see if any of the

121    paths in the initial model should be deleted, and we dropped non-significant associations from

122    the original hypothetical model. The resulting model, called the "final model",  was then re-

123    estimated **(Figure 2).** We used standardized regression coefficients (β) to assess the strength of

124    association between the variables (effect). Total, direct, and indirect effects of each variable on

125    HPV vaccine uptake were estimated (a direct effect represents a path coefficient, an indirect

126    effect represents the product of sequential path coefficients, and a total effect represents the

127    sum of direct and indirect effects).

128    We used Cohen's recommendations to interpret the relative size effect of the standardized

129    coefficients (a β value varying around 0.1 is considered as low, a value varying around 0.3 as

130    moderate, and a value greater than 0.5 as large) (23). To evaluate the goodness-of-fit between

131    the final model and the data, we used the comparative fit index (CFI), the standardized root

132    mean square residual (SRMR), and the root-mean-square error of approximation (RMSEA)

133    including 90%-confidence interval (90%CI). Values for CFI >0.94 suggest a good fit between data

134    and path models, whereas SRMR and RMSEA values less than 0.090 suggest acceptable fit, and

135    values less than 0.055 suggest good model fit (24).

136    All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary North

137    Carolina), and p-values below 0.05 were considered statistically significant.

**Ethics statement**

The Vaccinoscopie® Survey is a healthcare market research undertaken by professional market researchers (IDM families) on behalf of a pharmaceutical company (GSK). It has been conducted in accordance with the legal and ethical guidelines issued jointly by the European Society for Opinion and Market Research (ESOMAR) and the International Chamber of Commerce (ICC), as well as the French law on computer data and freedom. It does not require ethical committee review.  It warrants the total confidentiality of collected data, which, in any case, cannot be used to any other end than the ones defined for the survey. Furthermore, each participant may stop answering the questionnaire at any time and refuse that some pieces of data to be processed. Study participants consented to IDM terms of use and privacy policy, which indicated that their data would be used anonymously. The Vaccinoscopy® data file was approved by the French National Committee for Data Protection (n°1551077, dated 08/12/2011).

# RESULTS

**Study sample**

The global Vaccinoscopie® Survey data set (2015 to 2018) included in total 2038 different respondent mothers. Of those, 89 (4.4%) declared having never been in the situation of searching for information regarding a vaccination they had hesitated about, leaving 1949 records for the present study. The mean (+/- SD) age of the survey respondents was 43.5 (±4.9) years. Approximately half of the participants had a level at high school diploma (baccalaureate) or two-year post high school diploma (49.6%) and had a monthly household income of over 2700 Euros (48.0%). The full characteristics of the study participants, together with their responses to the survey questionnaire, can be found in **Table 1.**

**HPV vaccine coverage**

The mean uptake of the first dose of HPV vaccine over the study period was 27.7% (23.7% in 2015, 23.5% in 2016, 30.3% in 2017 and 33.1% in 2018). The full 2-dose regimen was completed in 18.7% of their daughters (14.4% in 2015, 16.1% in 2016, 21.3% in 2017 and 22.6% in 2018).

## Internet and other sources of vaccine information

Approximately 24% of the mothers declared using the Internet as a source of vaccine information. This medium was the third most frequently cited source of information reported by the mothers, after the family physician (91.8%) and the relatives/family/friends (26.1%), and before the pharmacist (14.9%) **(Table 1)**.

## Logistic regression analysis

The uptake of the first dose of HPV vaccine was lower among daughters of the mothers who indicated using the Internet as a source of vaccine information compared to daughters of those who indicated not using it: 18% compared to 31%, respectively (P<0.0001). In multivariate analysis adjusted for physician recommendation of HPV vaccination, attitudes towards vaccines in general, perception of HPV vaccine usefulness, maternal level of education, geographical region of residence, and the year of the survey, the use of the Internet as a source of vaccine information was significantly associated with a lower HPV vaccination (aOR=0.66; 95% CI, 0.47-0.91) **(Table 2)**.

## Path analysis

The results of the path analysis modeling are depicted in **Figure 2.** The estimated « final model » shows a good overall fit: CFI=0.97, SRMR=0.03 and RMSEA=0.02, 90%CI (0.02-0.03). Overall, 26 % of the variance in HPV vaccine uptake was explained by the model. **Table 3** shows the direct, indirect, and total effects of Internet use and other sources of information on HPV vaccine uptake (effects of other variables are reported in the **Supplementary Table**). The total effect of Internet use on HPV vaccine uptake was proved to be significant and negative. It is considered as low ($\beta$=-0.10, Standard Error (SE)=0.02, P<0.0001), and represents in absolute value 27% of the highest total effect on HPV vaccine uptake, which is observed with the physician recommendation of HPV vaccination ($\beta$=0.37, SE=0.01, P<0.0001) **(Table 3 and Supplementary Table).**

A total of 4 paths were significant to explain the relationship between Internet use and HPV vaccine uptake:

191      1)   Internet use -> perceived level of information regarding childhood vaccination->

192         attitudes towards vaccines in general -> perception of HPV vaccination usefulness ->

193         HPV vaccination;

194      2)   Internet use -> perceived level of information regarding childhood vaccination ->

195         attitudes towards vaccines in general -> HPV vaccination;

196      3)   Internet use -> attitudes towards vaccines in general -> perception of HPV vaccination

197         usefulness -> HPV vaccination;

198      4)   Internet use -> attitudes towards vaccines in general -> HPV vaccination (**Figure 2**).

199

200 Internet use was also found to mediate the negative effect of the « family and friends » source

201 of information on HPV vaccine uptake ($\beta$=-0.10, SE=0.02, P<0.0001), as Internet use was

202 positively associated with this source of information ($\beta$=0.10, SE=0.02, P<0.0001). In reverse,

203 Internet use was negatively associated with the «family physician» source of information ($\beta$=-

204 0.28, SE=0.03, P<0.0001), which was found to have a total positive effect on HPV vaccine uptake

205 ($\beta$=0.08, SE=0.01, P<0.0001).

## DISCUSSION

207 The spread of false information online and its influence on vaccination have been frequently

208 addressed in the literature. However, the quantification of the effect of Internet use as a

209 resource for answering questions on vaccination on actual vaccine uptake is much less

210 documented. We found that maternal search for vaccine information in the Internet was

211 associated with a lower HPV vaccination initiation by their daughters. This result is congruent

212 with the findings of the 2016 French National Health Barometer, in which parents of children

213 aged 1 to 15 who relied uniquely on the Internet for information on vaccination were less likely

214 to vaccinate their children against diphtheria, tetanus, and pertussis (25). Path analysis further

215 confirmed the negative effect of Internet use on HPV vaccine uptake ($\beta$=-0.10, SE=0.02,

216 P<0.0001). The analysis further revealed how Internet mediated its effect through a lower

217 perceived level of information on childhood vaccination (which could be explained by the

218 confusion resulting from contradicting pieces of information found on the Internet),

219 unfavorable attitudes towards vaccination in general, and a lower perceived level of HPV

220 vaccine usefulness. This effect runs contrary to the positive effect of obtaining information from

221 a family physician ($\beta=0.08$, SE=0.01, P<0.0001), through more favorable attitudes towards

222 vaccines and higher perception of HPV vaccine usefulness.

223 The Internet affords unprecedented opportunities for finding answers to health questions, but

224 also poses some challenges for its users. Parents should take complete responsibility to base

225 their vaccination decision on accurate information, wisely and consciously choosing their

226 sources of information whenever questions arise as to the benefit, efficacy or safety of any

227 given vaccine. Until each and every parent is equipped with the necessary knowledge and skills

228 to interrogate the Internet safely, healthcare providers remain the most suitable and accurate

229 sources of information on the topic of vaccination, and parents should be encouraged to seek

230 information primarily from them. Interventions should be designed to empower parents to

231 better recognize mis/disinformation, and consult only reputable sources of information if they

232 wish to go online. In any case, the need to question the veracity of the information retrieved

233 online should be emphasized, as it is sometimes not easy to distinguish between trustworthy

234 and questionable websites.

## Strengths and limitations

235

236 To the best of our knowledge, this is the first study investigating the association between

237 Internet use as a source of information by vaccine-hesitant mothers and the uptake of HPV

238 vaccine by their daughters. A key strength of this study is the use of path analysis to examine

239 specific pathways by which Internet use among vaccine-hesitant mothers is associated with a

240 lack of HPV uptake by their daughters, beyond the traditional logistic regression approach which

241 only allows quantification of the association between two variables, all others things being

242 equal.

243 The following limitations should be considered when interpreting the results of this study. First,

244 the exposure measure was related to the behavior of seeking online information for vaccines in

245 general, rather than HPV vaccine specifically. Nevertheless, only HPV vaccination is

246 recommended in the target's age group of the daughters in the surveyed sample, hence most

247   probably the source of questioning among their mothers. Second, the quota sampling approach

248   employed for the recruitment of the mothers in the Vaccinoscopie® Survey allows a study

249   sample that is representative of the general population with respect to specific criteria (SPC,

250   geographic region of residence and number of children), but does not ensure that it is

251   representative of the general population with regard to other criteria. Therefore, caution is

252   warranted when generalizing the results of the responding sample to the broader French

253   population. In particular, confidence intervals and P-values have to be very carefully

254   interpreted: they would apply if the data were obtained from a random probability sample.

255   Furthermore, there is a possibility of selection bias through self-selection of participants, and

256   also because the Internet population might not be fully representative of the general population

257   (excluding the most disadvantaged groups and/or the non-French-speaking immigrants). Third,

258   some factors possibly intervening in the process unfolding between Internet use and HPV

259   vaccine uptake were not questioned in Vaccinoscopie® Survey and could not be introduced in

260   our model. In a Delphi survey based on the World Health Organisation Strategy Advisory Group

261   of Experts framework of vaccine hesitancy, we have shown that the factors possibly determining

262   HPV vaccine uptake in France are numerous (26). These include, for example, vaccine

263   knowledge, perception of the safety of the vaccine, and trust issues towards the health system.

264   This may explain the direct effect observed of Internet use on HPV vaccine uptake, which

265   probably indicates a residual effect not captured by the model variables, rather than a genuine

266   direct effect. Fourth, this analysis was based on cross-sectional data. Therefore, causal

267   inferences cannot be drawn, and reverse links between some variables cannot be completely

268   ruled out. For example, the association between Internet use and perceived level of information

269   on childhood vaccination may be due to reciprocal effects. Despite these limitations, this study

270   seems to confirm the detrimental impact of Internet use as a source of vaccine information in

271   vaccine-hesitant mothers. Additional studies are needed using prospective study designs among

272   a random sample of parents.

## CONCLUSION

274   In conclusion, this study found a weak but significant association between vaccine-hesitant

275   mothers' use of the Internet as a source of vaccine information and a lack of HPV vaccine uptake

276   by their daughters, through a lower perceived level of HPV vaccine usefulness, a lower

277   perceived level of information on childhood vaccination, and unfavorable attitudes towards

278   vaccination in general. While further studies are needed to confirm this link, there is no doubt

279   on the need to raise awareness about the importance of seeking information from a healthcare

280   provider, and consulting only reputable sources of information on the Internet.

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## 357    Tables

358    **Table 1.**  Distribution of study variables among 1949 vaccine-hesitant mothers (Vaccinoscopie®
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360    **Table 2.**  Results of bivariate and multivariate logistic regression analysis exploring the factors
361    associated with HPV vaccination (weighted data).

362    **Table 3.** Total, direct, and indirect effects of the Internet and other sources of information on
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364    **Supplementary table.**  Total, direct, and indirect effects of variables other than sources of
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367    **Figure 1.**  Conceptual model with the hypothesized interrelationships between the variables.

368    **Figure 2.**  Final model of associations with standardized path coefficients.

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## Author's contributions

FD and PC had designed the study. FD had performed the data analysis, the redaction of the manuscript, and the revision process of this paper based on Vaccinsoscopie Survey data acquired by OL. PC, OL, PM and LL have participated in the revision process and the redaction of the manuscript. GSK and IDM had no role in the study design nor in the data analysis. All authors have approved the final manuscript which was reviewed by GSK before submission.

## Conflict of interest

FD declares that MSD vaccines have covered registration fees, transport and accommodation costs for attendance to a conference in 2018 and received a research grant. PM was an investigator on projects that received funding from GSK and MSD for the evaluation of HPV vaccines in Africa. OL declares punctual interventions and support during conferences with Pfizer, MSD, Sanofi Pasteur, Janssen and GSK. PC declares no conflict of interest.