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1 **An agent-based model to simulate co-infection with human papillo-**
2 **maviruses in a partially vaccinated partnership network**

3

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19 **Abstract.** Human papillomaviruses (HPV) are among the most common sexually transmitted
20 infection and a necessary cause of cervical cancer. In the context of vaccination against a sub-
21 group of genotypes, better understanding the role of biological interactions between HPV
22 genotypes and social interactions between humans is essential to anticipate what the vaccine
23 impact could be at the population level. Existing models that study interactions between gen-
24 otypes are based on basic homogeneous assumptions about human-to-human transmission,
25 whereas agent-based models that take into account the heterogeneity of human behavior and
26 transmission do not consider possible interactions between genotypes. Here, we present a
27 novel stochastic agent-based model formalizing the co-circulation on a human partnership
28 network of multiple interacting genotypes, some of them being preventable by the vaccine
29 (vaccine types) and others not. The model explicitly formalizes heterogeneity in sexual behav-
30 iors and makes it possible to explore distinct genotypic interaction mechanisms during intra-
31 host co-infections. Using model simulations, we investigate infection dynamics in the popula-
32 tion after vaccine introduction depending on assumptions regarding vaccine coverage and
33 vaccine and non-vaccine genotype interactions.

34

35 **Keywords:** agent-based model, simulation, human papillomavirus, vaccination, transmission,
36 genotype interactions.

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38

39 **1 Introduction**

40 Mathematical models are useful tools to understand the dynamics of infectious disease
41 spread in human populations and predict the impact of control strategies such as screening or
42 immunization programs. Compartmental models are a classical form of models for studying
43 infection transmission, in which individuals are grouped indiscriminately in compartments ac-
44 cording to their infectious status (e.g., susceptible, infected, recovered). In the context of sex-
45 ually transmitted infections, the assumption of homogeneous sexual behaviors underlying
46 compartmental models is unrealistic, as informed by surveys showing high heterogeneity
47 across individuals and ages (Bajos and Bozon 2008). Agent-based models (ABMs) appear to be
48 the most suitable to reproduce the heterogeneity of individual behaviors and simulate their
49 effects on a population scale (Auchincloss and Diez Roux 2008). They also facilitate the mod-
50 elling of co-circulation of several pathogens, which is made complicated by the use of com-
51 partmental models.

52

53 In this paper, we present a model specifically applied to the simulation of between-human
54 transmissions of genital infections with human papillomavirus (HPV). HPV infections are
55 among the most common sexually transmitted infections, especially in younger people, and
56 could lead to the development of cancers around the age of 50 years (Walboomers et al. 1999;
57 de Sanjosé et al. 2007). Vaccination protecting against prolonged HPV infection was intro-
58 duced in 2007. However, available vaccines are not universal. They protect against a fraction
59 of HPV genotypes only (called vaccine types). Anticipating the impact of vaccination on the

60 global evolution of HPV infection at the population level therefore requires integrating as-
61 sumptions regarding how circulating genotypes, and in particular vaccine and non-vaccine
62 types, interact for host infection, which was not done before. We propose here a new ABM
63 combining a heterogenous contact network and between-genotypes interactions and apply it
64 to the French context.

65 The paper is organized as follows. After discussing existing works, we describe the specifica-
66 tions of the new agent-based model we developed. We then present results from experi-
67 mental simulations and finally provide a discussion on our model and results.

68 **2 Related works**

69 Only few models of HPV transmission have formalized potential interactions between geno-
70 types (Elbasha et al. 2008; Pons-Salort et al. 2013; Murall et al. 2014; Man et al. 2020). Elbasha
71 and Galvani studied the conditions of coexistence of two genotypes at equilibrium before vac-
72 cine introduction as a function of the baseline reproduction number (number of secondary
73 infections generated by the introduction of an infected individual) of each genotype (Elbasha
74 et al. 2008). Murall *et al.* questioned the evolutionary response of genotypes to the selection
75 pressure imposed by the immune response induced by vaccination (Murall et al. 2014). Pons-
76 Salort *et al.* examined the influence of co-infection dynamics (simultaneous or sequential elim-
77 ination of co-infections) on the evolution of non-vaccine prevalences after vaccination and
78 also addressed the issue of genotype replacement, i.e. an increased prevalence of genotypes
79 not included in the vaccine following vaccine introduction (Pons-Salort et al. 2013). In partic-
80 ular, they find that in the case of simultaneous clearance, genotypic replacement is always
81 observed regardless of the nature of the interaction between the genotypes. Finally, Man *et*

82 *al.* sought to determine whether type replacement could be observed in early post-vaccina-
83 tion surveillance (Man et al. 2020). However, these former models are all based on the as-
84 sumption that sexual contacts are homogeneous. It is likely that the diversity of behaviors has
85 a marked impact on the dynamics of co-circulation of genotypes at the population level since
86 it affects the risk of infection (Shiboski and Padian 1996). Therefore, faithful replication of
87 sexual behaviors is essential to correctly interpret observations of HPV prevalences and pro-
88 vide more accurate projections of the epidemiological and ecological consequences of vac-
89 cination. Among the possible modelling approaches, the ABM seems to be the most appropri-
90 ate to reproduce the heterogeneity of individual behaviors and to simulate their effects at the
91 population level (Auchincloss and Diez Roux 2008). Many ABMs have been developed follow-
92 ing the introduction of vaccines to study the effectiveness and cost-effectiveness of vaccina-
93 tion and/or screening (Olsen and Jepsen 2010; Van de Velde et al. 2012; Burger et al. 2018).
94 However, existing ABMs have not considered possible interactions between genotypes (Olsen
95 and Jepsen 2010; Van de Velde et al. 2012; Matthijse et al. 2015; Burger et al. 2018; Johnson
96 et al. 2018). We therefore undertook to develop our own model and to adapt it to the French
97 context.

98 **3 Methods**

99 The model description follows the ODD (Overview, Design concepts, and Details) protocol as
100 defined by Grimm et al. (Grimm et al. 2006). We developed a multi-agent system to support
101 the process of HPV genotype transmission in the population. The global architecture of the
102 multi-agent system has been developed in C++ (version 4.9.0). In addition to classical elements
103 of models developed in object programming, the program includes two other components:

104 (1) a component for the agent (as detailed later), in which the agent's characteristics and re-
105 lated processes (to become infected, to start or to finish a partnership, to eliminate the infec-
106 tion, etc.) are defined; and (2) a component for the population (as detailed later), in which the
107 variables of the environment of the agents are defined and which allows to initiate the pro-
108 cesses (demography, partnership, infectious process, etc.) for all agents at each time step.
109 Simulations were run on the computational and storage services (TARS cluster) provided by
110 the IT Department at Institut Pasteur, Paris. Statistical analyses and graphics were computed
111 using R (version 3.5.2).

112 **3.1 Overview of the model**

113 **Purpose.** The ABM simulates a virtual population of individuals in heterosexual partnership
114 and the co-circulation of distinct HPV genotypes in interaction. A vaccination campaign is also
115 simulated, assuming that vaccinated individuals are protected against a portion of genotypes
116 only (called "vaccine types", VT) whereas their infectious risk to the rest of the circulating
117 types (called "non vaccine types", NVT) is not altered. The main goal is to understand how
118 vaccination affects the global infection dynamics in the presence of between-genotype inter-
119 actions on a heterogeneous partnership network.

120 **State variables and scales.** The agents are human individuals characterized by a set of varia-
121 bles listed in Table 1 and described below. Each agent is explicitly modeled and characterized
122 by his/her sex, age, sexual activity class (number of partners he or she will have during the
123 year), partnership status (in three categories - virgin, with a partner, or single), vaccination

124 status, and infection status for each genotype g (in four categories - susceptible to (infection
 125 with) g , infected with g , naturally immune to g , or vaccinated if g is a VT).

126 **Table 1.** Individual variables characterizing each agent

Variable	Type	Update time
ID	Code number	At entrance
Sex	Boolean	At entrance
Age	Number weeks	At each time step
Vaccination status	Boolean	At entrance
Variables related to partnership process		
Sexual activity class	Integer	At 15, 17, 19 and 24 years
No partner during the current year	Boolean	On the first day of each year
Partnership status	String	At the beginning and at the end of partnership
Partner ID	Pointer	At the beginning and at the end of partnership
End date of partnership or inactivity	Simulation week number	At the beginning and at the end of partnership
Counter of partners during the current year	Integer	At the onset of new partnership; and at reset on first day of each year
Counter of partners over the simulation	Integer	At the onset of new partnership
Variables related to the infection process – for each genotype g		
Infection status	String	At the beginning and at the end of infection and immunity
End date for infection	Simulation week number	At the onset of infection
Natural immunity status	String	At the end of infection
End date for natural immunity	Simulation week number	At the end of infection
Counter of infections over the simulation	Integer	At the onset of infection

127

128 *Environmental variables.* Agents share a number of environmental variables characterizing the
 129 population as presented in Table 2 and detailed in the following sections. In most countries,
 130 anti-HPV vaccination was first recommended only for young females before the age of 15
 131 years with possible catch-up generally until 18, with no vaccination of males (Baylor 2006;

132 ECDC 2020). We therefore assumed here that only females were vaccinated, and that vaccina-
 133 tion occurred before their entrance in the model.

134 **Table 2.** Environmental variables characterizing the population and their values

Description	Default value	Rationale
Population size (N)	800,000 individuals	For computational purposes
Population age range	From 15 to 30 years of age	Fixed, corresponding to HPV infection peak
Variables related to partnership process		
Age at first partnership	Normal distribution with mean 17.5 years in females, 16.8 in male	Mean, calibrated on (Bajos and Bozon 2008)
Distribution of individuals by sexual activity class	According to sex and age (Table 3 in appendix)	From (Bajos and Bozon 2008) and calibrated
Proportion of individuals without a partner during the year	According to sex and age (Table 3 in appendix)	From (Bajos and Bozon 2008) and fixed
Duration of partnership	According to sexual activity class and age (Table 3 in appendix)	Mean, from (Bajos and Bozon 2008) and calibrated
Duration of inactivity between two partnerships	According to sexual activity class (Table 3 in appendix)	Mean, calibrated
Frequency of sexual intercourse within a relationship	2 per week	Arbitrary
Duration of partner search before mixing between sexual activity groups	According to sexual activity class (Table 3 in appendix)	Calibrated
Maximum proportion of individuals changing from one extreme class to another at ages 17, 19 and 24	95% for females and 45% for males	Calibrated
Variables related to infection process		
Number of genotypes	2 vaccine types (VT) 12 non-vaccine types (NVT)	According to genotypes reported in (Markowitz et al. 2013)
Transmission probability parameter for VT and NVT genotypes	$\beta_V = 0.16$ per sexual act (VT) $\beta_{NV} = 0.125$ per sexual act (NVT)	Calibrated
Duration of infection	Exponential distribution with mean 52 weeks	From (Trottier et al. 2006)
Duration of immunity	Exponential distribution with mean 12 weeks	Calibrated
Genotype interaction parameter (γ)	1	To be varied
Initial probability of infection	0.2 for NVT and 0.08 for VT	Arbitrary
Initial probability of co-infection among those initially infected	0.4 for any first genotype g	Arbitrary
Date of vaccine introduction	After 70 years of simulation	To ensure prevalence equilibrium is reached
Vaccine coverage	60% of females by age cohort	To be varied

135 *Scales.* The model time step is the week. A simulation year lasts 52 weeks. Agents are not ex-
136 plicitly distributed in space.

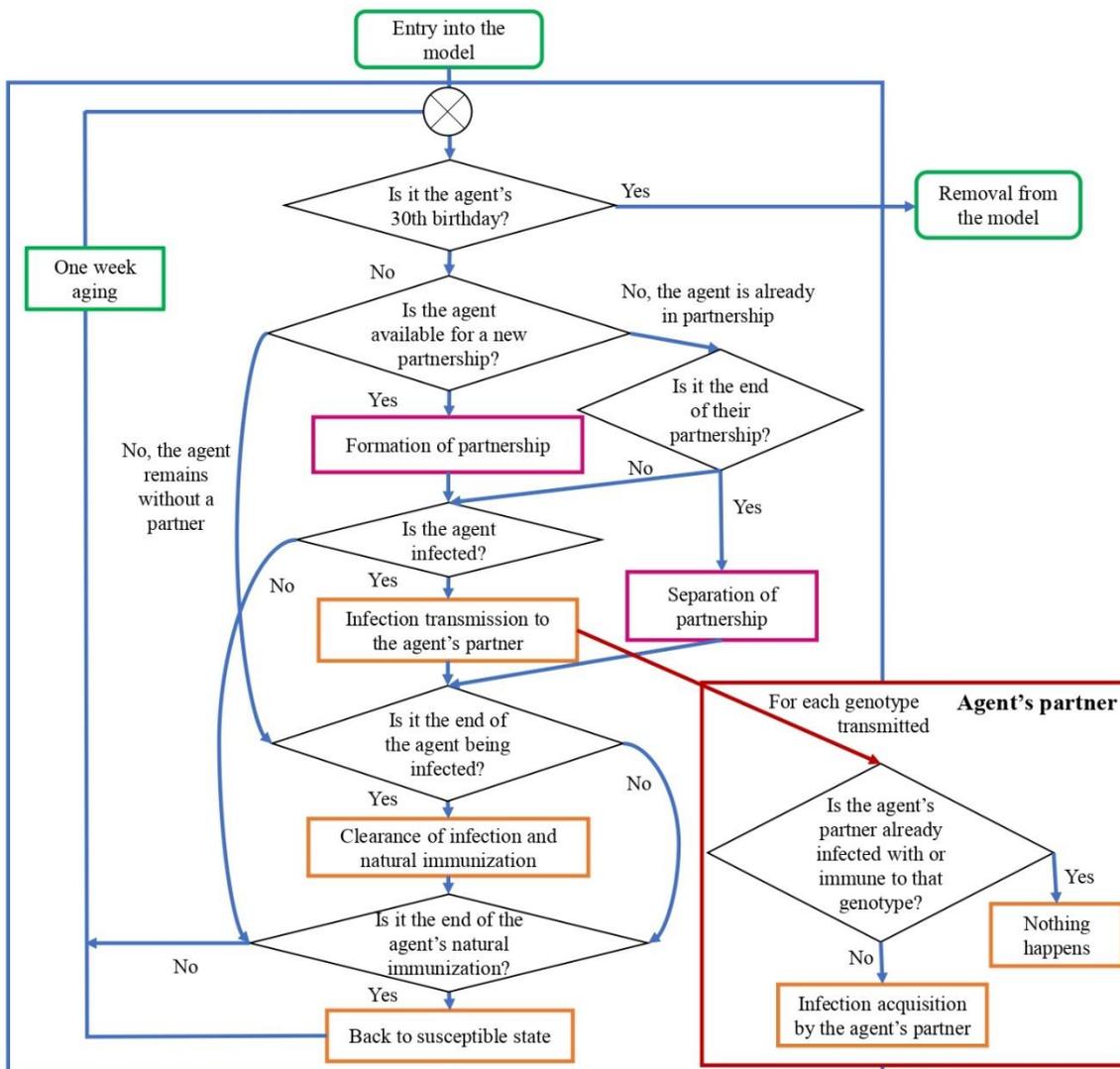
137

138 **Process overview and scheduling.** The model proceeds in several processes which are sequen-
139 tially updated on a weekly or yearly basis, depending on the processes, as detailed below.
140 Figure 1 summarizes the execution of the three major weekly processes in the model: demo-
141 graphic, partnership and infection processes.

142 *Demographic process.* Agents age one week with every time step. On the day they turn 30
143 years, agents leave the model. When an agent exits the population, he/she is directly replaced
144 by a new 15-year-old individual with an equal probability of being male or female, to ensure
145 the population remains stable over time. At inclusion the agent's states and counters are ini-
146 tialized. Sexual activity class and date of first partnership are drawn from probabilistic distri-
147 butions (see Table 2). In addition, if a vaccination campaign is in progress at a female's entry
148 date, she will be vaccinated according to a probability defined by vaccine coverage, protecting
149 her against VT genotypes with 100% efficacy for at least 15 years.

150 *Partnership process.* Every week, the list of agents available for a new relationship is updated;
151 each agent from this list then searches for a new partner according to his/her sexual activity
152 class and age. If the agent has been waiting on the list for a predefined period of time without
153 finding a partner within his/her sexual activity class, he/she is allowed to search within other
154 sexual activity classes. If a partner is found, a duration of partnership is drawn according to

155 the agent's sexual activity class and age (Table 3 in appendix). When the end date of a part-
 156 nership is reached, the partnership is split. For each of the two agents involved, a duration of
 157 inactivity is drawn according to his/her sexual activity class, defining the date for the agent to
 158 become again available for a new partnership and be included in the list mentioned above.



159 **Fig. 1. Schematic representation of the ordered weekly processes that could occur for each**
 160 **agent under conditions.**
 161

162 In green the demographic process, in pink the partnership process and in orange the infec-
 163 tion process

165 *Infection process and natural disease history.* At each time step, the model proceeds with in-
166 fection transmission. For each genotype g , all partnerships characterized by one partner in-
167 fected with g and one partner susceptible to g are evaluated: transmission of g from the in-
168 fected to the susceptible partner occurs with a transmission probability parameter β_V or β_{NV}
169 depending on whether genotype g belongs to VT or NVT group, respectively. If an infection
170 occurs, the duration of infection is drawn from an exponential distribution (Table 2). In a sec-
171 ond step, the model proceeds with the evolution of infection status for all infected agents. For
172 any genotype g , all agents infected with g who reach their date of recovery change their in-
173 fection status: they become immune to genotype g and cannot transmit genotype g anymore.
174 Acquired natural immunity is assumed to confer total protection against genotype g for a lim-
175 ited duration which is drawn from an exponential distribution (Table 2). All immunized agents
176 reaching the end date of their immunized status become fully susceptible to genotype g again.

177

178 The processes scheduled annually are executed on the first day of the year in the following
179 order:

180 *Reset of counters of annual number of partners.* For each agent of the model, the counter of
181 his/her cumulative number of partners over the current year is set to 0.

182 *Change of sexual activity class.* A portion of agents aged 17, 19 and 24 years and not engaged
183 in long partnerships (i.e., >1 year) are randomly selected to change sexual activity class to
184 conform to age groups available in the survey data and changing sexual behavior with age.
185 Changing from one extreme class to the other is limited to a maximum proportion of individ-
186 uals by sex (Table 2) to favor evolution between adjacent sexual activity classes. Numbers are

187 drawn to match the targeted distribution of sexual activity classes by age category. Addition-
188 ally, in all sexual activity classes, a fraction of agents who will have no partner over the coming
189 year is randomly selected (Table 2).

190 **3.2 Design Concept**

191 **Interaction**

192 *Inter-agent contacts.* Interactions between agents occur through heterosexual partnership.
193 The agent's sexual activity class defines the number of partners the agent will have during the
194 year. Partnerships between agents from the same sexual activity class are promoted, although
195 mixing between classes is allowed after several weeks and unsuccessful trials to find a partner
196 within the same sexual activity class (Table 2). When a partnership is set, the two partners
197 involved are assumed to be in contacts at an arbitrary frequency of two sexual intercours-
198 es per week over the partnership duration. Simultaneous partnership is not allowed in the
199 model.

200 *Inter-agent transmission.* An agent infected with a genotype g can transmit g at any time dur-
201 ing partnership with transmission probability β_V or β_{NV} per act, if his/her partner is not already
202 infected with g nor naturally immunized to g .

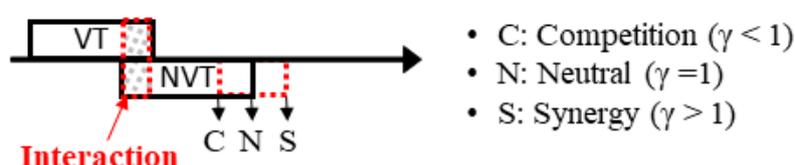
203 *Within-agent ecological interaction between genotypes.* When two genotypes simultaneously
204 infect an agent, interaction between genotypes may occur. This interaction is assumed to af-
205 fect the duration of infection with one of the genotypes. Interactions are defined unidirection-
206 ally: we only consider the impact of the presence of VT on the epidemiological characteristics
207 of NVT. Indeed, we assume that, if an agent already infected with a vaccine genotype g_V is

208 subsequently infected with a non-vaccine genotype g_{NV} , the average duration of infection
 209 D_{INF}^{eff} with g_{NV} is modified by a multiplicative factor γ , called the strength of interaction (pre-
 210 sented in Eqs 1 and in Fig. 2).

$$D_{INF}^{eff}(g_{NV}) = D_{INF}(g_{NV}) \times \gamma \quad (1)$$

211 Both competitive, whereby $\gamma < 1$, *i.e.*, the presence of VT reduces duration of infection with
 212 NVT, and synergistic interaction, whereby $\gamma > 1$, *i.e.*, the presence of VT enhances the duration
 213 of infection with NVT, are allowed. Since the period of infection coincides with the period of
 214 possible transmission, this also has an impact on the length of time the infected agent can
 215 transmit g_{NV} .

216



217 **Fig. 2. Schematic representation of the interaction mechanism between VT and NVT during**
 218 **an agent co-infection.**

219 Here the agent is first infected with VT and subsequently acquires NVT. The interaction alters
 220 the duration of infection with NVT by a multiplicative factor γ , the strength of interaction.
 221 The vertical arrows indicate varying recovery times depending on the interaction. C: compet-
 222 itive, N: neutral, S: synergistic

223

224 **Stochasticity.** The model is stochastic, stochasticity being included both through the definition
 225 of random parameters and through random processes. Sexual activity class, age at first part-
 226 nership, age difference between partners, and all durations (of partnership, of inactivity be-

227 tween two partnerships, of infection, of immunization after vaccine introduction) are ran-
228 domly drawn from probability distributions (Table 2). Finding a partner, changing sexual activ-
229 ity class and getting infected are defined as random processes.

230 **Observations.** A large variety of data can be collected from model simulations. For the pur-
231 pose of this article, we record for every agent, at each time step, his/her sexual behavior (num-
232 ber of partners during the past year and lifetime) and his/her infection characteristics. Be-
233 cause we aim at monitoring the dynamics of infection at the population level, we aggregate
234 agent data according to human characteristics to obtain numbers of infected agents by age,
235 sex, sexual activity class, etc.

236 **3.3 Details on the processes**

237 **Initialization.** Model initialization is achieved in successive steps. First, all environmental var-
238 iables are initialized, as detailed in Table 2. Then all agents are created, with their partnership
239 and infection statuses and counters initialized. At initialization, sex and age of each agent are
240 randomly drawn to ensure homogeneous distribution of population across sex and age. Sexual
241 activity class and age at first partnership are drawn from probabilistic distributions (if the
242 agent is older than his/her age at first partnership, he/she can directly look for a partner).
243 Infection status with respect to VT and NVT is randomly drawn according to the probabilities
244 of infection and co-infection defined for initialization (Table 2). Those initial probabilities are
245 set to arbitrary non null values without any impact on prevalence equilibrium.

246 **4 Results**

247 **4.1 Data**

248 **Partnership data.** We used data reported in a French survey published in 2008 entitled *Con-*
249 *texte de la Sexualité en France* (CSF) (Bajos and Bozon 2008) to define relevant parameters
250 characterizing the partnership process and calibrated the model to reproduce realistic contact
251 patterns in the country. This population-based cross-sectional survey provides information on
252 sexual behaviors of a representative sample of 12 364 French males and females. We notably
253 used data on the distribution of individuals in sexual activity classes by age categories (18-19,
254 20-24 and 25-29 years old), the distribution of individuals without partner during the year by
255 age categories, age at first partnership, age difference between partners, duration of partner-
256 ship, and duration of inactivity between two partnerships.

257

258 **Infection data.** Because no data in the general population were available on the proportions
259 of individuals infected with HPV by age and genotype in the pre-vaccine era in France, we used
260 distributions reported from an epidemiological study carried out in the US (Markowitz et al.
261 2013), a country in which HPV epidemiology has been suggested to be similar to that in France
262 (de Sanjosé et al. 2007; Bruni et al. 2010). From (Markowitz et al. 2013) we extracted HPV
263 prevalence (*i.e.*, the proportion of individuals infected in the population) of VT (gathering 2
264 genotypes: HPV 16 and 18) and NVT (gathering 12 genotypes: HPV 31, 33, 35, 39, 45, 51, 52,
265 56, 58, 59, 66 and 68) in the pre-vaccine era for females by age group (14-19, 20-24 and 25-
266 29 years old). We calibrated model parameters related to the infection process assuming no
267 genotypic interaction (strength $\gamma = 1$). These included transmission probability parameters θ_v

268 and β_{NV} and the mean duration of immunity for all genotypes (default values are presented in
269 Table 2). For each interaction scenario, calibration was repeated for β_{NV} in order to properly
270 fit pre-vaccine NVT prevalence.

271 **4.2 Input and simulations**

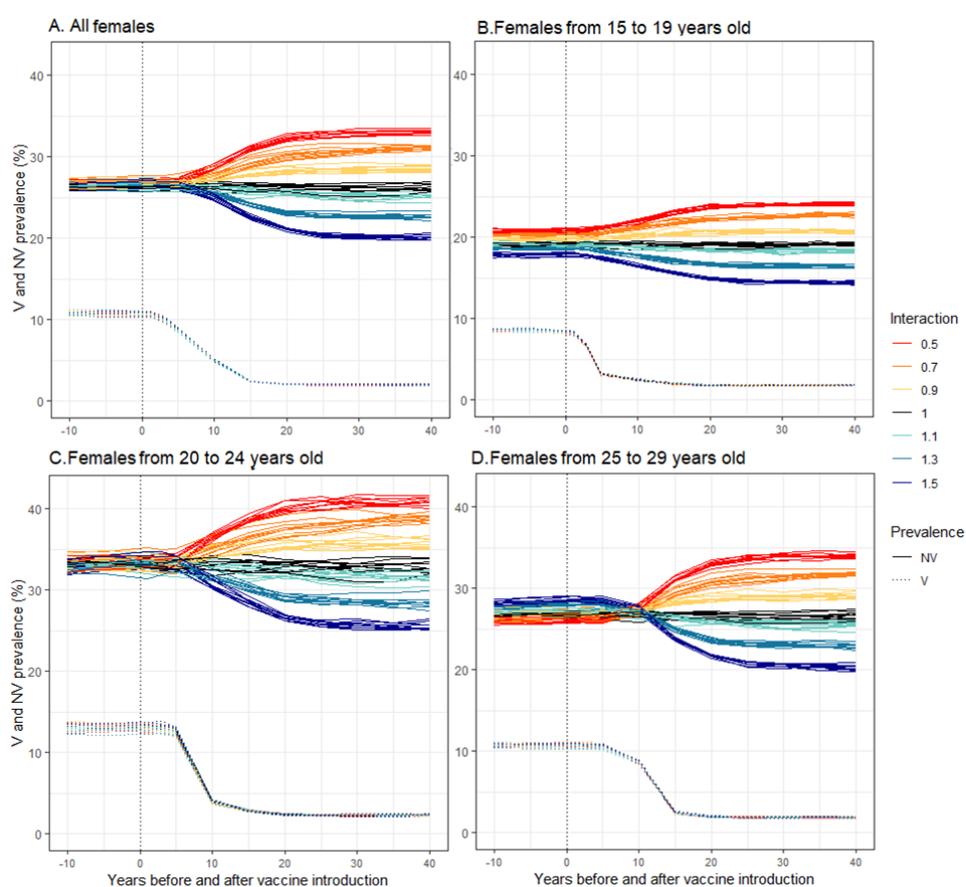
272 The model was initialized with 800,000 individual agents interconnected through a contact
273 network. We experiment 7 interaction scenarios (0.5, 0.7, 0.9, 1, 1.1, 1.3, 1.5) with 10 simula-
274 tions each. The explored genotypic interaction values and the corresponding transmission
275 rates are given as input to the model. First the simulations are run for 70 years to reach prev-
276 alence equilibrium in the pre-vaccination period. Vaccination is introduced at date 70 years,
277 post-vaccination time is then defined as $t=0$ year, assuming 60% vaccine coverage. The model
278 is simulated over 40 years post-vaccine introduction. The execution of a single simulation over
279 110 years takes about 2 hours. The 10 independent stochastic simulations of each scenario
280 are generated thanks to a bash code taking the explored parameter values as input and run in
281 parallel on the cluster nodes. Sensitivity analyses were also carried out to evaluate the impact
282 of our model assumptions on observed results.

283 **4.3 Output**

284 Fig. 3 displays the dynamics of VT and NVT prevalence before and after vaccine introduction
285 for 10 independent repetitions of the model in seven distinct scenarios of between-genotype
286 interaction.

287 **Vaccine impact on VT prevalence.** Before vaccine introduction, the model was able to repro-
288 duce realistic VT prevalence patterns, with an average 10.7% in females. The prevalence was

289 slightly higher in the age group 20-24 years old than in the other groups and lowest in 15-19
 290 year olds. After vaccine introduction, an expected decrease of VT prevalence was observed in
 291 females, which stabilized to a new equilibrium (3.2%) once the age cohort had had a chance
 292 to be immunized (after 5 years among 15-19 year olds up to 15 years among 25-29 year olds).
 293 All calibrated interaction scenarios yielded undistinguishable patterns of VT prevalence and
 294 stochasticity was weak, as demonstrated by the limited variability across the 10 simulations
 295 displayed for VT prevalence in Fig. 3.



296 **Fig. 3. Temporal evolution of the prevalence of NVT and VT genotypes according to inter-**
 297 **action scenarios**

298 Proportion of infected of NVT (upper plain line curves) and VT (lower dashed curves) geno-
 299 types according to interaction scenarios (colors) (A) All females; (B) Females aged 15 to 19
 300 years; (C) Females aged 20 to 24 years; (D) Females aged 25 to 29 years. The vaccine is of-
 301 fered from $t = 0$ to all females <15 years of age with 60% vaccine coverage. For each interac-
 302 tion scenario, results of 10 simulations are displayed.

303 **Vaccine impact on NVT prevalence.** The model also satisfactorily reproduced NVT prevalence
304 before vaccine introduction, reaching an average 26.5% in females. The same pattern of NVT
305 prevalence was seen across age groups as with VT. Minor differences were visible across cali-
306 brated interaction scenarios. Stochasticity was more pronounced for NVT than for VT geno-
307 types, particularly in the 20-24 age group, but standard deviations remained limited to <4% in
308 all scenarios.

309 After vaccine introduction, the evolution of NVT prevalence strongly depended on the inter-
310 action scenario (Fig. 2). In the absence of genotypic interaction (neutral scenario), NVT preva-
311 lence remained constant over time, while in non-neutral interaction scenarios some dynamics
312 was observed at the population level. Under competitive interaction ($\gamma < 1$), NVT prevalence
313 increased while, conversely, under synergistic interaction ($\gamma > 1$), NVT prevalence decreased
314 over time until reaching a new equilibrium. The magnitude of prevalence variations depended
315 on the strength of interaction: the more it deviated from 1, the more NVT prevalence deviated
316 from pre-vaccine equilibrium. The magnitude of the increase or decrease also appeared to be
317 proportional to NVT prevalence before vaccine introduction. Indeed, variations in NVT preva-
318 lence appeared to be most pronounced in 20-24 year old females who also had the highest
319 prevalence before vaccine introduction. Times to reach the new prevalence equilibrium was
320 the same for NVT and VT.

321 **Sensitivity analyses.** With respect to the partnership process, combinations of parameter val-
322 ues that best minimized the calibration criteria after the chosen ones resulted in VT and NVT
323 prevalence curves changing at the same time and with comparable magnitude. For the infec-

324 tion process, modifying one of the parameter values, whether it is the mean duration of infec-
325 tion, the mean duration of immunity or the transmission probabilities of the VT and NVT, af-
326 fects VT and NVT prevalence equilibrium quantitatively but not the overall qualitative dynam-
327 ics following the introduction of the vaccine.

328 **5 Discussion**

329 In this paper, we introduce a new agent-based model simulating the co-circulation of vaccine
330 and non-vaccine genotypes in a heterogeneous human population. The main originality of this
331 ABM is to consider genotype interactions. The agent-based approach makes it possible to de-
332 fine precisely natural history of HPV infection as well as co-infections in individuals and to
333 assess vaccine impact on the overall dynamics of HPV infection at the population level.

334 The illustration that we present is an example of how the model can be used to simulate VT
335 and NVT prevalence according to genotypic interaction scenarios and prevention measures
336 such as vaccination. Successively calibrated interaction scenarios help investigate how syner-
337 gistic interactions between genotypes could contribute to the decrease in overall HPV preva-
338 lence aimed by vaccine introduction. Conversely, we show that competitive interactions may
339 lead to substantial increase in NVT prevalence: because VT prevalence decreases following
340 vaccination introduction, so does the prevalence of VT and NVT coinfections, resulting in
341 longer duration of infection with NVT and more opportunities for NVT transmission. This eco-
342 logical replacement can potentially minimize the decrease in or even increase overall HPV
343 prevalence, therefore limiting vaccine benefit at the population level.

344 Although vaccination coverage is much lower in France (around 20%), we have chosen to pre-
345 sent here a scenario with 60% vaccination coverage for a better observation of the replace-
346 ment phenomenon. With lower vaccination coverage, variations in NVT prevalence are still
347 visible under non-neutral interactions, but with reduced magnitude (results not shown).

348 We also chose a fixed population of 800,000 individuals, a size typical of a big metropolitan
349 area such as Paris, to avoid additional complexity of modelling spatial constraints on contact
350 mixing. Considering such a large population yields more stable results and allows us to inves-
351 tigate subpopulations such as age groups in Fig. 3. Due to strong heterogeneity in contacts
352 across ages and sexual activity classes, simulating smaller populations may lead to more vari-
353 ability and possible extinctions of the infectious process, making any calibration difficult. Sim-
354 ulating the real French population size (~9,200,000 individuals 18-30 years of age) would re-
355 quire extremely long calculation times and would only slightly reduce the already limited var-
356 iability we observe in our results.

357 Despite a detailed agent-based approach is used here, some simplifications and assumptions
358 were made to compensate for the lack of data and gaps in knowledge. Several limitations
359 should be underlined.

360 First, it was not possible to calibrate the model simultaneously to sexual behaviors reported
361 by males and females, as distributions of numbers of partners did not match. In the CSF survey,
362 more males declared large numbers of partners than females (Bajos and Bozon 2008). Report-
363 ing bias differential by sex has been observed in previous studies (Fenton et al. 2001; Mitchell
364 et al. 2019) and may explain part of our calibration difficulties. To overcome those difficulties,
365 we focused on females' data in order to adapt the model and the estimation parameters, while

366 trying to make it consistent with males' data in terms of cumulative number of partners. More-
367 over, because our interest was to simulate realistic heterogeneous contact patterns than can
368 reproduce the typical bell-shaped curve of HPV prevalence according to age, we did not con-
369 sider any temporal variation in sexual behaviors. Although the model was run for decades
370 assuming unrealistically stable behaviors, that step only aimed at reaching prevalence equi-
371 librium before the introduction of the vaccination and further analysis of the post vaccination
372 dynamics was restricted to 40 years.

373 Second, to keep our model relatively simple, only two transmission probability parameters
374 were estimated for VT and NVT genotypes, thus mimicking average dynamics across the two
375 VT and the 12 NVT genotypes, respectively. However, large differences in prevalence are re-
376 ported not only between VT and NVT groups, but also within each group (Markowitz et al.
377 2013). It could therefore be relevant to simulate VT and NVT genotypes more finely by cali-
378 brating transmission probability parameters by genotype. It would then be possible to study
379 each genotype individually as well as to simulate interactions more precisely, for example be-
380 tween certain defined genotypes.

381 Finally, simulation results presented here were restricted to the assumption that genotypic
382 interaction would affect the infection duration of a second acquired virus. Interaction mecha-
383 nisms between HPV genotypes remain unknown and could as well involve viral load and/or
384 cell-infection ability (McLaughlin-Drubin and Meyers 2004; Xi et al. 2009; Biryukov and Meyers
385 2018). Alternative mechanism interaction scenarios were therefore incorporated in the model
386 code, affecting probability of acquisition. Such mechanisms could be explored in the future to
387 measure their population-level impact on prevalence and compare their credibility.

388 In conclusion, our model formalizing both the heterogeneity of sexual behaviors at the popu-
389 lation level and the co-circulation of distinct groups of genotypes allows us to evaluate path-
390 ogen transmission dynamics in realistic sexual networks. In the context of HPV transmission,
391 our simulation results show that interactions between HPV genotypes can significantly impact
392 effectiveness of anti-HPV vaccination at reducing HPV prevalence. This model can be used to
393 further investigate the impact of most recent anti-HPV vaccines targeting a larger number of
394 genotypes, again altering prevalence equilibrium, as well as the recent extension of vaccina-
395 tion to males (starting in 2021 in France). Vaccination of boys is expected to increase the mag-
396 nitude and speed of change in the prevalence of VT and NVT. Finally, the model could easily
397 be adapted to study other research questions related to sexually transmitted pathogens and
398 their interactions.

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411 Abbreviations

412 ABM(s), Agent-based model(s); HPV, human papillomavirus; ODD, Overview, Design concepts,
413 and Details; VT, vaccine type; NVT, non-vaccine type.

414 Availability of data and materials

415 All the source codes of the model and those for the analyses are available on request.

416 Competing interests

417 LO reports research grants from Pfizer through her institution, unrelated to the submitted
418 work. All other authors report no competing interests.

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423 Authors' contributions

424 MB, MF, EDA, ACMT and LO conceptualized the project. ACMT and LO supervised the project.
425 MB, ACMT and LO designed the model. MB and MF developed the model. MB, ACMT and LO
426 performed the validation of the model and the experimental simulations. All the authors re-
427 viewed the article and approved the submission.

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431 **Appendix**432 **Table 3.** Complementary values of variables related to the partnership process according to
433 sexual activity class and possibly age and sex

Sex	Age (years)	Number of partners per year			
		1	2-3	≥4	0 ^a
Distribution of individuals by sexual activity class (%)					
Female	15-17	85.00 (calibrated) ^b	12.00 (calibrated)	3.00 (calibrated)	3.63 (fixed)
	18-19	68.99	24.72	6.29	3.63
	20-24	75.84	21.56	2.60	7.24
	25-29	85.75	11.07	3.18	5.59
Male	15-17	75.00 (calibrated)	19.00 (calibrated)	6.00 (calibrated)	14.38 (fixed)
	18-19	60.42	27.59	11.99	14.38
	20-24	61.85	28.15	10.00	10.89
	25-29	76.30	17.23	6.47	6.69
Duration of partnership					
Any	15-19	4 categories (<1, 1-4, 5-9 and >10 years) distributed as in (Bajos and Bozon 2008) ^c (mean 224 weeks)	Gamma distribution with calibrated mean 14 weeks (fixed variance 8)	Gamma distribution with calibrated mean 4 weeks (fixed variance 5) ^d	Not relevant
	20-24	4 categories distributed as in (Bajos and Bozon 2008) ^c (mean 264 weeks)			
	25-29	4 categories distributed as in (Bajos and Bozon 2008) ^c (mean 440 weeks)			
Duration of inactivity between two partnerships					
Any	All	Uniform distribution [1:104] weeks	Gamma distribution with calibrated mean 14 weeks (fixed variance 8)	Gamma distribution with calibrated mean 4 weeks (fixed variance 5) ^d	At least 52 weeks
Duration of partner search before mixing between sexual activity classes					
Any	All	10 weeks (calibrated)	5 weeks (calibrated)	30 weeks (calibrated)	Not relevant

434 ^a Individuals without a partner are randomly selected each year from the population;435 ^b When not specified fixed or calibrated, values are extracted from (Bajos and Bozon 2008);436 ^c One category of partnership duration is drawn from a multinomial distribution whose parameters are the proportions reported in (Bajos and Bozon 2008), then a precise value is drawn from a uniform distribution within the duration category;437 ^d The duration of partnership and between two partnerships are identical in most sexually active individuals and
440 drawn only once a year:

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