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Revisiting Assumptions about Age-Based Mixing Representations in Mathematical Models of Sexually Transmitted Infections

CW Easterly¹, F Alarid-Escudero, PhD², EA Enns, PhD², and S Kulasingam, PhD³

¹Macalester College

²Division of Health Policy and Management, School of Public Health, University of Minnesota, Twin Cities

³Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Twin Cities

Abstract

Background—Sexual mixing between heterogeneous population subgroups is an integral component of mathematical models of sexually transmitted infections (STIs). This study compares the fit of different mixing representations to survey data and the impact of different mixing assumptions on the predicted benefits of hypothetical human papillomavirus (HPV) vaccine strategies.

Methods—We compared novel empirical (data-driven) age mixing structures with the more commonly-used assortative-proportionate (A-P) mixing structure. The A-P mixing structure assumes that a proportion of sexual contacts – known as the assortativity constant, typically estimated from survey data or calibrated – occur exclusively within one’s own age group and the remainder mixes proportionately among all age groups. The empirical age mixing structure was estimated from the National Survey on Sexual Attitudes and Lifestyles 3 (Natsal-3) using regression methods, and the assortativity constant was estimated from Natsal-3 as well. Using a simplified HPV transmission model under each mixing assumption, we calibrated the model to British HPV16 prevalence data, then estimated the reduction in steady-state prevalence and the number of infections averted due to expanding HPV vaccination from 12-through-26-year-old females alone to 12-year-old males or 27- to 39-year-old females.

Results—Empirical mixing provided a better fit to the Natsal-3 data than the best-fitting A-P structure. Using the model with empirical mixing as a reference, the model using the A-P structure

Corresponding Author: Fernando Alarid-Escudero MS, PhD, alari006@umn.edu, Division of Health Policy and Management, University of Minnesota School of Public Health, 420 Delaware Street SE, MMC 729, Minneapolis, MN, 55455.

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often under- or overestimated the benefits of vaccination, in one case overestimating by 2-fold the number of infections prevented due to extended female catch-up in a high vaccine uptake setting.

Conclusions—An empirical mixing structure more accurately represents sexual mixing survey data, and using the less accurate, yet commonly-used A-P structure has a notable effect on estimates of HPV vaccination benefits. This underscores the need for mixing structures that are less dependent on unverified assumptions and are directly informed by sexual behavior data.

Keywords

mathematical modelling; sexually transmitted infections; human papillomavirus; sexual behavior; sexual mixing

Introduction

Mathematical models are widely used to evaluate interventions for sexually transmitted infections (STIs), including pre-exposure prophylaxis for human immunodeficiency virus (HIV) [1], vaccination against human papillomavirus (HPV) [2–4], and theoretical vaccination against gonorrhea and chlamydia [5–7]. A key component of STI models is the sexual mixing structure, which describes the probability of sexual contact between individuals, often grouped by demographic and behavioral characteristics like age and level of sexual risk behaviors.

Modelers often assume that, in any given population, sex partner choice lies somewhere between total assortativity – choosing sex partners only from one’s own subpopulation – and total proportionality [8,9], where the probability of mixing with a given subpopulation is the proportion of the total partnerships that are offered by that subpopulation. Historically, modelers attempted to capture these extremes and the continuum in between with the assortative-proportionate (A-P) mixing structure, parameterized by the assortativity constant (usually ϵ) which reflects the proportion of sexual partners who are selected within one’s own subpopulation. The remaining proportion, $1 - \epsilon$, are selected proportionally from the entire population, including one’s own subgroup [5]. A-P mixing has been widely used in STI models due to its simplicity and ease of parametrization – in a recent model meta-analysis paper [10], 9 out of the 15 HPV disease models for which sufficient detail could be retrieved used an A-P mixing structure to represent age mixing [2,11–19].

However, it is unclear whether A-P mixing accurately reflects the observed patterns of sexual mixing reported in sexual behavior surveys, even when the parameter ϵ is estimated from survey data, due to the strict and perhaps unnecessary assumptions it makes about the form of the mixing structure. Sexual behavior surveys such as the National Survey on Family Growth (NSFG) in the United States [20] and the National Survey on Sexual Attitudes and Lifestyles (Natsal) in the United Kingdom [21] collect a variety of sexual behavior data from respondents, including characteristics of their most recent sexual partners. Age mixing is particularly amenable to direct estimation from these surveys because respondents are likely to know a sexual partner’s age.

In this study, we evaluated the fit of the A-P mixing structure to the Natsal sexual behavior data and compared it to an empirical mixing structure that does not make the A-P assumption. We then used these two mixing structures in a mathematical model of HPV transmission and evaluated how the age mixing assumptions impacted model-predicted benefits of expanding vaccination beyond 12-to-26-year-old females, measuring the reduction in HPV prevalence and number of HPV infections averted.

Methods

Overview

We first estimated A-P and empirical mixing structures from the Natsal sex survey data, then compared their goodness-of-fit (GoF) to the data. We then used each structure in an HPV transmission model to quantify the benefits of different policies to expand HPV vaccination beyond the currently recommended target population of 12- to 26-year-old females [22]. In particular, we evaluated the impact of expanding HPV vaccination from females alone to 12-year-old males and extending the maximum age for female catch-up vaccination from 26 to 39 years of age. We measured the benefits of vaccination in terms of the reduction in HPV steady-state prevalence and the number of infections averted over 50 years.

Data sources

We analyzed data from the most recent available wave of the National Survey on Sexual Attitudes and Lifestyles (Natsal-3), which was conducted in the United Kingdom from 2010-2012 [21]. The survey, a probability sample of British 16- to 74-year-olds, was administered face-to-face, with a self-completion portion for the more sensitive questions. Natsal-3 included 15,162 respondents, of whom 12,526 had ever had heterosexual anal, oral, or vaginal intercourse. Sexually experienced respondents reported the ages of up to three of their most recent sexual partners (over the respondents' lifetime) as well as their own age at the time of first sexual contact with each partner. Each reported partnership was treated as a separate data point, which yielded a total of 18,303 sexual partnerships.

Estimation of age-mixing parameters

The details of the A-P [13,23] and empirical [24,25] mixing structures are included in the Appendix. The mixing matrix from [13] was used because it is the most recent formulation of the A-P structure and improved upon that in [23]. In the empirical mixing structure, an age mixing matrix is multiplied by an A-P sexual activity mixing matrix. The methods used to estimate the empirical age mixing matrix itself are novel to our study.

In the empirical mixing estimation, we used regression methods to estimate the sex-specific mean and variance of survey respondents' partners' ages ("partner age") conditioned on the age of the respondents ("chooser age"). We fit three regression models: a standard linear model with normally distributed errors and generalized linear models (GLM) with Gamma-distributed errors and either an identity or a log link. We used the Akaike Information Criterion [26] to quantify the models' goodness-of-fit (GoF) and selected the model with the lowest AIC as our representative empirical mixing structure. To estimate the parameter governing the degree of age assortativity in the A-P structure (e_{AM} and e_{AF} for male and

female), we identified values for ϵ that maximized the likelihood of observing the Natsal-3 age mixing data. The A-P assortativity constant depends on the definition of the age groups, so we performed the fitting procedure with four specifications of age groups – the age groups used in the model (defined below), and evenly-spaced groups of 2 years, 5 years, and 10 years.

Finally, we compared the GoF of the best-fitting empirical structure and the A-P structure to the Natsal-3 data, defined in this case as the negative log likelihood (NFF) of observing the data under the given model, where a smaller NFF indicates a better fit. An R [27] package to perform these analyses on any heterosexual mixing data is available at <https://github.com/caleb-easterly/mixage>.

Mathematical Model of HPV Transmission

We developed a deterministic, ODE-based age- and sexual-activity-structured model of HPV transmission in a heterosexual population, based on previously published models [3,23]. The model included susceptible, infected, recovered, vaccinated, breakthrough infection (vaccinated yet infected), and vaccinated and recovered from breakthrough infection health states (Figure 1). We divided the population into 3 sexual activity groups (high, medium, and low activity) and 18 age groups (12, 13-15, 16-17, 18-19, 20-21, 22-24, 25-26, 27-29, 30-31, 32-34, 35-36, 37-39, 40-44, 45-49, 50-54, 55-59, 60-64, and 65-73). Susceptible individuals become infected through sexual contact with infected individuals, the rate of which was estimated using the age-specific number of new sexual partners reported in Natsal-3 and the different age mixing structures described in the previous section. Once infected, individuals recover based on the duration of HPV infection. Recovered individuals return to the susceptible state based on the duration of natural immunity. The prior distributions for the natural history of HPV infection was parameterized for HPV type 16, the most prevalent oncogenic type [28], and then calibrated to prevaccination HPV16 prevalence data from Britain [29]. The full model equations and parameter information are in the Appendix.

Calibration

Some parameters of the mathematical model, like the per-partnership transmission probability and the duration of natural immunity, cannot be informed directly by observed data, so we estimated the parameters by calibrating the transmission models (empirical and A-P) to age-specific pre-vaccination prevalence of HPV16 in Britain [29]. To account for potential non-identifiability, we adopted a Bayesian framework [30]. Briefly, we defined prior distributions on parameters of interest, then used incremental mixture importance sampling (IMIS) [31,32] to estimate posterior distributions of the parameters conditional on the prevalence data.

To propagate the uncertainty of all parameters to the outcomes of interest, we performed a probabilistic sensitivity analysis (PSA) [33,34]. PSA samples were drawn from the IMIS posterior distributions for calibrated parameters and from pre-defined probability distributions for non-calibrated parameters. We evaluated the models for each of 1,000 randomly sampled parameter sets, then calculated the reduction in number of infections and in steady-state prevalence, as outlined below. Point estimates are reported as the median of

the simulations, with the associated interquartile range (25th to 75th percentile). The Appendix contains prior distributions and calibrated values for the calibrated parameters and sensitivity analysis distributions for the non-calibrated parameters.

Vaccine Expansion Policy Evaluation

We used the HPV transmission model to evaluate the impact of different age mixing structures on the predicted benefits of expansions of HPV vaccination beyond 12-to-26-year-old females, by either expanding vaccination to 12-year-old males or allowing catch-up vaccination in previously unvaccinated 26-to-39-year-old females. Vaccine uptake among these expanded age groups was modeled following the assumption that unvaccinated individuals were progressively less likely to become vaccinated as they aged (as in [2]).

We explored the benefits of extending vaccination to males while assuming one of four uptake scenarios for 12-year-old females: 30%, 50%, 70%, or 90%. These are referred to as M30, M50, M70, and M90, respectively. To estimate the benefit of extending vaccination to 26-to-39-year-old females, we calculated the reduction in prevalence under the same 12-year-old female uptake assumptions without male vaccination: these are referred to as “extended female 30” (EF30), EF50, EF70, and EF90. All vaccination strategies are presented in Table 1.

We defined the average reduction in steady-state prevalence $R_{k,c,r}$ as [3]:

$$R_{k,c,r} = \frac{P_{k,r} - P_{k,c}}{P_{k,r}} \times 100 \quad \#(1)$$

where $P_{k,r}$ and $P_{k,c}$ denote the steady-state prevalence for age group a and gender k for reference and comparison vaccination strategies r and c .

We measured the reduction in the total number of HPV infections over 50 years by:

- 1) Running the model to steady-state under a reference strategy r ,
- 2) Using the steady-state as time 0, defining $C_{k,r}$ as the number of infections per 100,000 individuals for gender k over 50 years under strategy r ; the same for strategy c is $C_{k,c}$
- 3) Calculating the number of infections prevented by strategy c :

$$RC_{k,c,r} = C_{k,r} - C_{k,c} \quad \#(2)$$

Results

Age Mixing Estimation

Out of the three linear models, the gamma GLM with the identity link had the lowest (best) AIC – 101,493 versus 102,451 (gamma with log link) and 117,895 (standard linear regression) – so we used it as our representative empirical model. Next, across all age group

assumptions, there was a greater likelihood of observing the Natsal-3 data when the gamma GLM empirical structure was assumed (Table 2): with the model age groups, the data had a negative log likelihood (NLL) of 36,267 under the empirical structure and 46,813 under the A-P structure (lower NLL corresponds to a higher likelihood, and thus better model fit).

The A-P structure and the best-fitting empirical age mixing structure are presented in Figure 2a. The predicted sexual mixing structures are plotted, stratified by sex, as the probability that an individual of age x (on the x -axis) selects a sex partner of the opposite sex of age y . The A-P mixing structure predicts a constant out-of-group probability for each age group, while the empirical structure using a gamma GLM regression better reproduces the variability in the Natsal-3 data. We also include examples of single age-group distributions in Figure 2b. In the following, we recognize that the empirical mixing better represents the data and use it as a reference.

Benefits of Vaccinating Males

We use “A-P model” and “empirical model” to refer to the HPV transmission model with A-P and empirical mixing structures, respectively. In general, the overall reduction in prevalence due to vaccinating males was similar across the two models, while the A-P model overestimated the reduction in infections, especially in males (Figure 3). The magnitude of the overestimate of reduction in infections in males stayed relatively constant as 12-year-old uptake increased ($R_{k,c,r} = 68\%$ with 30% coverage and 61% with 90% coverage), while the A-P estimate for females went from an underestimate to an overestimate ($R_{k,c,r} = -21\%$ and 21% for 30% and 90% coverage, respectively). In the M90 scenario, the A-P model predicted that vaccination would prevent 17,847 (IQR: 15,632-20,110) (male) and 5528 (IQR: 4,775-6,250) (female) infections per 100,000 people over 50 years, while the empirical model predicted 11,096 (IQR: 9,351-13,195) and 4,563 (IQR: 3,669-5,644) fewer infections for males and females. This corresponds to an A-P model overestimate of 61% and 21% for males and females, respectively.

Catch-Up Vaccination for 26- to 39-year-old Women

At high vaccine uptake, the A-P model predicted a prevalence reduction nearly equal to the empirical model prediction, while it predicted somewhat lower reductions at 30% and 50% uptake (Figure 4). In the 30% uptake scenario, EF30, the A-P model predicted that extended female catchup would cause a 0.11 (IQR: 0.093-0.13) and 0.40 (IQR: 0.36-0.45) percent reduction in average prevalence in males and females, respectively, while the empirical model predicted a 0.17 (IQR: 0.14-0.19) and 0.49 (IQR: 0.45-0.53) percent reduction for males and females.

A greater difference was again seen in the number of infections averted than in the steady-state prevalence. The A-P underestimated the infections prevented in females by extended female vaccination at low uptake and overestimated infections prevented in females at high uptake. The A-P also overestimated the infections prevented in males for all vaccine scenarios. In the EF90 scenario, the A-P model predicted 222 (IQR: 174-272) and 260 (IQR: 215-313) infections prevented for males and females, respectively, per 100,000 individuals over 50 years, while the empirical model predicted 110 (IQR: 82-140) and 191 (IQR:

152-254) infections averted. Thus, the A-P model overestimated the number of infections prevented in the EF90 scenario by 102% for males and 36% for females.

Discussion

In this study, we compared the goodness-of-fit to survey data of the assortative-proportionate (A-P) mixing structure and a more realistic regression-based mixing structure, which was itself determined by comparing several regression methods. Using a mathematical model of HPV infection, we computed the benefits of a theoretical vaccination program when each of the two different sexual mixing structures was assumed. We believe this is the first study to quantify the effects of using the A-P structure rather than a better-fitting empirical structure on the model-estimated benefits of an HPV prevention strategy. Our results are applicable to any STI model that incorporates sexual contact and age.

Our results show that regression estimates of mean and variance of partner age fit sexual behavior survey data better than the A-P structure, while making more realistic assumptions about sexual mixing. For example, the empirical structure predicted that, in general, people partner with those close to their own age, while the A-P structure predicted a higher-than-observed probability of partnership between much older and much younger people. The assortativity parameter of the A-P only modifies the probability of partnering with one's exact age group; otherwise, the higher sexual activity observed in younger people results in an increase in the probability of partnering with them relative to the rest of the population. For example, there were no partnerships reported between 65-to-73-year-old women and 18-to-29-year-old men in the Natsal-3 survey, but the A-P structure predicts a 37% probability that a 65-to-73-year-old woman chooses an 18-to-29-year man as a sex partner. The probability in the empirical structure, 0.04%, is much more accurate.

Different age mixing structures led to notably different estimates of HPV vaccine benefits. Overall, the model using the A-P structure overestimated the benefits of vaccination, up to a more than 2-fold overestimate of the number of infections prevented in men due to catch-up vaccination for 26-to-39-year-old females. Extending vaccination to females led to somewhat larger discrepancies between the two mixing structures than introducing male vaccination, which suggests that modeling studies using an A-P mixing structure may be particularly likely to overestimate benefits of age-based programs, such as those that evaluate age-targeted educational campaigns, the optimal age at which to start or stop vaccination, or enhanced access to STI prevention services for specific demographic groups.

A limitation of this study is the relative simplicity of the model, which did not include separate HPV types or further disease states such as cervical intraepithelial neoplasia and cancer. However, the specification of the mixing structure most directly impacts transmission, and the simpler model structure used here allows for easier isolation of the effects of the A-P structure in transmission models. In addition, we did not consider other factors that may drive age preferences in sex partners, such as level of sexual activity or other risk factors, and, as such, developing more sophisticated regression models for age mixing should be investigated further. Furthermore, a national survey like Natsal-3 does not

supply knowledge of sexual networks on a local scale, the structure of which can also impact model estimates.

While the A-P mixing structure has been used successfully to represent partner choice between sexual activity groups, detailed sex survey data indicate this type of structure does not accurately represent partner choice by age. More generally, A-P structures do not consider preferences for ages, sexual activities, or geographic locations similar to but not exactly the same as one's own. When a characteristic, like age, contains a notion of 'distance' (for example, 18 years old is closer to 20 years old than to 60 years old), it is important to use mixing structures that can accommodate preferences for close but not identical demographic groups. The empirical mixing structure can represent the age mixing of any population based on available data and should be the first choice for representing age mixing in an STI model when detailed age mixing survey data are available. In settings where sexual behavior data is lacking, performing surveys like Natsal-3 to estimate mixing patterns with greater certainty can reduce the likelihood of making sub-optimal policy recommendations.

In this study, we showed that different sexual mixing structures can yield different benefits of interventions in sexual transmission models. Mixing structures that accurately reflect the observed sexual mixing are an essential component of mathematical models of STIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

SPAR	sex partner acquisition rate, or the number of new partners in a given time period.
Natsal-3	National Survey on Sexual Attitudes and Lifestyles, third wave (conducted 2010-2012)
A-P	assortative-proportionate, a type of mixing structure.

GoF	goodness-of-fit, a measure of how well a model represents data.
NLL	negative log likelihood

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Figure 1:
Model flow diagram

Figure 2. Comparisons between the mixing structures.

- (a) The estimated mixing structures compared to the Natsal-3 data, assuming evenly-spaced 4-year age groups. For each age group on the x-axis, the shaded values indicate a probability distribution of partners' ages (y-axis).
- (b) Different estimates of the distribution of partner's ages for 40-to-44-year-old females, assuming 4-year age groups.

Figure 3 –. Benefits of male vaccination by mixing structure.

Please note that the y-axis may be different for males and females to enable better comparison between A-P and empirical mixing structures.

- (a) Relative reduction in steady-state prevalence by mixing structure and vaccination strategy.
- (b) Reduction in number of cases over 50 years due to vaccination of young males.

Figure 4: Benefits of extended female catch-up by mixing structure.

Please note that the y-axis is different for males and females to enable better comparison between A-P and empirical mixing structures.

- (a) Relative reduction in steady-state prevalence due to vaccinating 26- to 39-year-old females, by vaccination strategy and mixing structure.
- (b) Cases prevented per 100,000 people over 50 years due to vaccinating 26- to 39-year-old females, by mixing structure and vaccination strategy.

Table 1:

Negative log likelihood (NLL) of observing the Natsal data given the mixing structure. Lower numbers indicate a greater probability of observing the Natsal data, thus a better fitting structure.

Age groups	Empirical NLL	A-P NLL
1 year	53,613	76,335
5 year	25,757	41,390
10 year	16,854	19,597
Model	36,267	46,813

Table 2.

Vaccination strategies, adapted from Chesson, et al., 2011[2], defined in terms of annual probability of completing a full 3-dose series of the HPV vaccine. The probabilities that change in the comparison strategy are bolded.

ANNUAL PROBABILITY OF VACCINATION BY AGE AND GENDER											
SCENARIO	STRATEGY	UPTAKE	M					F			
			12	13-17	18-26	27-39	12	13-17	18-26	27-39	
M30	Reference	Low	0	0	0	0	30	5	2.5	0	
	Comparison	Low	30	0	0	0	30	5	2.5	0	
M50	Reference	Medium	0	0	0	0	50	10	5	0	
	Comparison	Medium	50	0	0	0	50	10	5	0	
M70	Reference	High	0	0	0	0	70	15	7.5	0	
	Comparison	High	70	0	0	0	70	15	7.5	0	
M90	Reference	Highest	0	0	0	0	90	20	10	0	
	Comparison	Highest	90	0	0	0	90	20	10	0	
EF30	Reference	Low	0	0	0	0	30	5	2.5	0	
	Comparison	Low	0	0	0	0	30	5	2.5	1.25	
EF50	Reference	Medium	0	0	0	0	50	10	5	0	
	Comparison	Medium	0	0	0	0	50	10	5	2.5	
EF70	Reference	High	0	0	0	0	70	15	7.5	0	
	Comparison	High	0	0	0	0	70	15	7.5	3.75	
EF90	Reference	Highest	0	0	0	0	90	20	10	0	
	Comparison	Highest	0	0	0	0	90	20	10	5	