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Title: A revision of sexual mixing matrices in models of sexually transmitted infection.

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Short title: Revision of the mixing matrix in STI models

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ABSTRACT

Two sexual mixing matrices previously used in models of sexually transmitted infections (STIs) are intended to calculate the probability of sexual interaction between age groups and sexual behaviour subgroups. When these matrices are used to specify multiple criteria for how people select sexual partners (such as age group and sexual behaviour class) their conditional probability structure means they have in practice been prone to misuse. We constructed revised mixing matrices that incorporate a corrected conditional probability structure and then used one of them to examine the effect of this revision on population modelling of STIs. Using a dynamic model of HPV transmission as an example, we examined changes to estimates of HPV prevalence and the relative reduction in age-standardised HPV incidence after the commencement of publicly-funded HPV vaccination in Australia. When all other model specifications were left unchanged, the revised mixing matrix initially led to estimates of age-specific oncogenic HPV prevalence that were up to 11% higher than our previous models. After re-calibrating the model by modifying unobservable parameters characterising HPV natural history, the revised mixing matrix yielded similar estimates to our previous models, predicting that vaccination would lead to relative HPV incidence reductions of 43% and 85% by 2010 and 2050 respectively, compared to 43% and 86% using the unrevised mixing matrix formulation. Our revised mixing matrix offers a rigorous alternative to commonly used mixing matrices, which can be used to reliably and explicitly accommodate conditional probabilities, with appropriate re-calibration of unobservable model parameters.

1. Introduction

Mathematical modelling of the spread of sexually transmitted infections (STIs) requires some mechanism to represent the probabilities of individuals having sexual contact with particular sub-categories of sexual partners. One such widely used mechanism is the 'mixing matrix' as described by Garnett *et al* [1]. The mixing matrix has been described and used in the modelling of the spread of HIV infection and for other infections such as gonorrhea and human papillomavirus (HPV) [1-5]. The elements of the mixing matrix represent the probabilities that people in a given subgroup of the population will form sexual partnerships with people in another given population subgroup. The resulting expected partnerships are then modelled as a pathway for STI transmission. Following Garnett [1], two commonly used population subgroups for defining mixing in the population are age group and level (hereon 'class') of sexual activity (specified, for example, by the average number of new partners per year); although in principle other criteria could also be used to subdivide the population, for example needle use [6].

Previous formulations of the mixing matrix have been specified to model more than one sub-group at a time by splitting individual elements in the mixing matrix into multiple factors, with one factor for each subgroup class (e.g. age, sexual activity)[1, 7]. However, as we describe in this paper, splitting the existing mixing matrix structure in this manner can lead to inconsistencies or errors which could potentially impact on model predictions. Mixing matrices of the type considered in this paper specify heterosexual partner preferences, where a mixing matrix is produced for each side of the partner equation (e.g. separate mixing matrices for men and women). Such mixing matrices will not necessarily generate partner preferences that match, so some partner preferences will be unrealised. To ensure that infection calculations only deal with realised partnerships, a process is carried out following calculation of the initial mixing matrices ('balancing') [8]. Errors in the structure of the initial mixing matrices will not be corrected by the balancing procedure, as the results of balancing depend on the values in the initial mixing matrices. This paper is concerned with the structure of the mixing matrix before balancing is carried out and the effect this has on final model predictions.

The objective of this analysis was to construct revised mixing matrices not subject to the identified inconsistencies or errors, and then apply one of these revised matrices to quantify the effects of the revision on population modelling of predicted HPV prevalence and the impact of HPV vaccination. We simulated HPV transmission and the effects of HPV vaccination using a previously described model of heterosexual HPV transmission in the Australian population [9] which had been further developed from an earlier model for Finland [10].

2. Reformulation of the mixing matrix

2.1 General form

In general terms, the heterosexual mixing matrix ρ_{kab} represents the probability that an individual of sex *k* in population subgroup *a* will choose a sexual partner of sex *k′* in population subgroup *b*. Here *a* and *b* may each represent several different indices, corresponding to multiple criteria for subdividing the population into groups. For example, if the population is subdivided by age and sexual activity, then the mixing matrix has the form ρ_{kihjm}, representing the probability that someone of sex *k* in age group *i* and sexual activity class *h* (with *i* and *h* replacing index *a*) will form a partnership with someone of sex *k′* in age group *j* and sexual activity class *m* (with *j* and *m* replacing index *b*). Refer to Table 1 for a summary of notation used throughout this paper.

[Table 1 about here]

For a mixing matrix whose elements are factorised, the conditional probability structure of the matrix must represent the dependence or independence of the input parameters that will be used to populate the matrix. For example, in the population to be modelled, does the probability of choosing a partner from a particular sexual activity class depend on which partner's age group is selected? If so, do the matrix element factors represent these probabilities correctly?

Consider a matrix representing a population subdivided by age and sexual activity class. If it is assumed that there are no other factors affecting partner selection (such as the choice of assortative or proportional mixing considered in Section 2.3), then the general form of such a factorised mixing matrix is either

$$\rho_{kihjm} = P(G_{k'jm}) = P(\alpha_{k'j})P(G_{k'jm} \mid \alpha_{k'j}) \qquad \ldots (1)$$

selecting partner's age then sexual activity class, or

$$\rho_{kihjm} = P(G_{k'jm}) = P(\sigma_{k'm})P(G_{k'jm} \mid \sigma_{k'm}) \qquad \ldots (2)$$

which selects partner's sexual activity class then partner's age. Here, $\alpha_{k'j}$ represents the event "a partner of sex *k'* is selected from age group *j*"; $\sigma_{k'm}$ the event "a partner of sex *k'* is selected from sexual activity class *m*"; and $G_{k'jm}$ the event "a partner of sex *k'* is selected from age group *j* and sexual activity class *m*".

Logically, equations 1 and 2 should be equal, as they represent the same probability. However, we have identified that this is not the case for some published factorised sexual mixing matrices. We examine one example in Section 2.5. Examination of the conditional probability structure of two published mixing matrices is the focus of the rest of Section 2 and of Section 3.

2.2 Revision of a simple factorised mixing matrix

van de Velde *et al* [7] used a mixing matrix with two factors in each matrix element, representing

- Preference for partner's sexual activity class, independent of partner's age (denoted Γ_{hm}, with activity class *h* choosing activity class *m*); and
- Preference for partner's age, independent of partner's sexual activity class (denoted Λ_{ihj}, with age group *i* and sexual activity class *h* choosing age group *j*).

The age selection factor Λ_{ihj} is populated by values that are not subdivided by partner's sexual activity class [7], so that Λ_{ihj} is independent of a partner's sexual activity class. However, the form of the sexual activity selection factor in that matrix is

$$\Gamma_{hm} = \frac{\sum_{\alpha=1}^{n_A} T_m(\alpha)}{\sum_{\beta=1}^{n_S}\sum_{\alpha=1}^{n_A} T_\beta(\alpha)} \qquad \ldots (3)$$

,

(Here $T_m(j)$ represents the preference-weighted number of partnerships offered by the subgroup of potential partners with age group j and sexual activity class m, n_A is the number of age groups and n_S the number of sexual activity classes.)

This form implies that this factor is derived from values that are functions of the preferred partner's age and sexual activity class. In this case the appropriate form for the mixing matrix is that of equation 1. However, the summations over age in the numerator and denominator of equation 3 mean that the sexual activity preference factor Γ_{hm} as defined is independent of partner's age.

The correct form for Γ_{hm}, explicitly defining preference for partner's sexual activity as conditional on partner's age, is

$$\Gamma_{hm} = P(G_{k'jm} \mid \alpha_{k'j}) = \frac{T_m(j)}{\sum_{\beta=1}^{n_S} T_\beta(j)}, \qquad \ldots(4)$$

as partner's age group j has already been selected by the factor Λ_{ihj}.

The mixing matrix employed by Elbasha et al [11] is of the same general form: an age selection factor independent of sexual activity level multiplied by a sexual activity selection factor independent of age. This matrix is constructed from parameters that are specified by both age and sexual activity level, so it should also use a conditional probability structure. As this matrix strongly resembles the matrix that we examine in Sections 2.5 and 2.6, the structure appropriate for this particular case is the structure that we develop as equation 16 in Section 3.3.

These examples demonstrate that elements of a mixing matrix can be correctly factorised according to different partner preference criteria only if attention is paid to the dependence of the factors on each other. In general, it is safest to assume that factors are not independent and to structure the mixing matrix accordingly, so that the matrix form does not rely on an assumption of independence which may not hold in the population to be modelled. We will now show that this limitation becomes more problematic for more complex factorisations of mixing matrices, and then propose a revised matrix definition that explicitly accommodates conditional probabilities.

2.3 A matrix for assortative and proportional mixing

Nold [12] introduced a mixing matrix which is a mixture of *assortative* and *proportional* mixing. In assortative mixing, people only choose partners from their own subgroup. In proportional mixing, the chance that people choose partners from any given subgroup is proportional to the total number of partnerships offered by members of that subgroup.

The general mixing matrix for assortative mixing captures the probability of someone of sex k in subgroup i randomly choosing a partner in subgroup j in terms of the Kronecker delta δ_{ij} (which has the value 1 when $i = j$ and 0 otherwise), as

$$\rho_{kij} = \delta_{ij} .$$

The mixing matrix for proportional mixing captures the probability of someone of sex k in subgroup i randomly choosing a partner in subgroup j out of all n population subgroups as

$$\rho_{kij} = \frac{P_j}{\sum_{h=1}^{n} P_h} = \frac{c_j N_j}{\sum_{h=1}^{n} c_h N_h} ,$$

where P_j is the total number of partnerships on offer in subgroup j, c_j is the average number of partnerships offered by members of population subgroup j and N_j is the number of individuals in population subgroup j.

Nold's mixing matrix [12] uses a parameter ε to weight the contribution of each type of mixing, as follows:

$$\rho_{kij} = \varepsilon\delta_{ij} + (1-\varepsilon)\frac{P_j}{\sum_{h=1}^{n} P_h} \qquad \ldots (5)$$

Here, ε is the fraction of the population who will choose a partner assortatively, while $(1-\varepsilon)$ is the remaining fraction who will make a proportional choice. (For later notational convenience (see equation 16), this use of ε is the opposite of that in Garnett *et al.* [1])

Since ε is the fraction of the population who will choose a partner assortatively, $(1-\varepsilon)$ represents the fraction whose partner choices are made proportionally.

If the mixing matrix in equation 5 represents a population stratified by age, the mixing matrix may be written as

$$\rho_{kij} = P(\alpha_{k'j})$$

$$= P(A_A)P(\alpha_{k'j} \mid A_A) + P(A_P)P(\alpha_{k'j} \mid A_P) \qquad \ldots (6)$$

where A_A represents the event "partner selection is made assortatively by age" and A_P represents the event "partner selection is made proportionally by age".

2.4 Combined assortative and proportional mixing

Nold's scheme may be extended to describe a mixture of assortative and proportional mixing involving multiple partner selection criteria. For example, a population subdivided by age group and sexual activity class may for the purpose of calculating partner choice probabilities be divided into four groups who choose their partners:

i. Assortatively by age and assortatively by sexual activity;

ii. Assortatively by age and proportionally by sexual activity;

iii. Proportionally by age and assortatively by sexual activity;

iv. Proportionally by age and proportionally by sexual activity.

The probability of an individual belonging to each of these groups (and thus choosing a partner in the specified way) is then defined using $\varepsilon^{(A)}$, the probability of assortative mixing by age and $\varepsilon^{(S)}$, the probability of assortative mixing by sexual activity class.

The combined assortative and proportional mixing model can be extended to more than two factors, as done by French *et al* [6] who modelled HIV transmission using a mixing matrix incorporating age, sexual activity and needle use, resulting in eight combinations of partner choice criteria.

2.5 A currently used mixing matrix combining assortative and proportional mixing with multiple selection criteria

Garnett *et al* extended Nold's scheme to model assortative and proportional mixing by both age and sexual activity class and also a specific pattern of mixing in which women prefer men approximately ten years their senior [1]. Considering only assortative and proportional mixing by both age and sexual activity class and excluding women's preference for men ten years older, the matrix described by Garnett *et al* takes the form

$$\rho_{kihjm} = \left(\varepsilon^{(A)}\delta_{ij} + (1-\varepsilon^{(A)}) \frac{\sum_{\beta=1}^{n_S} P_{k'j\beta}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S} P_{k'\alpha\beta}} \right) \left(\varepsilon^{(S)}\delta_{hm} + (1-\varepsilon^{(S)}) \frac{P_{k'jm}}{\sum_{\beta=1}^{n_S} P_{k'j\beta}} \right), \qquad \dots (7)$$

where $P_{k'jm}$ is the number of partnerships on offer by people of sex *k'* in age group *j* and sexual activity class *m* and ρ_{kihjm} represents the probability that someone of sex *k* in age group *i* and sexual activity class *h* will form a partnership with someone of sex *k'* in age group *j* and sexual activity class *m*.

Here the first factor represents the age mixing component and the second the sexual activity mixing component, i.e. a partner's age is selected first, and then their sexual activity class.

Note that in this form of the mixing matrix, $\varepsilon^{(A)}$ and $\varepsilon^{(S)}$ are assumed to be constant across the entire population i.e. they are independent of all parameters defining both people making a partner choice and people being chosen as partners. In particular, $\varepsilon^{(A)}$ is independent of partner's sexual activity class and $\varepsilon^{(S)}$ is independent of partner's age.

2.6 Inconsistencies with assumptions

The following assumptions are implicit in Garnett's mixing matrix shown in equation 7:

Assumption 1: As described earlier, the parameters $\varepsilon^{(A)}$ and $\varepsilon^{(S)}$ are treated as constants, and thus $\varepsilon^{(A)}$ is independent of partner's sexual activity class and $\varepsilon^{(S)}$ is independent of partner's age;

Assumption 2: The events A_A and S_A (partner's age and sexual activity class chosen assortatively) are independent of each other – without this, factorisation is not possible. All mixing matrices considered from here on satisfy this assumption.

Also, this mixing matrix should satisfy the following condition:

Condition 1: The probability value ρ_{kihjm} should not depend on whether it is calculated by specifying the partner's age group or sexual activity class first, as in either case the same probability is being calculated.

However, we found that under Assumptions 1 and 2, the mixing matrix in equation 7 cannot satisfy Condition 1.

We identified this inconsistency as follows. Equation 7 can be written in a form similar to equation 6 (where partner's age group is selected before their sexual activity class):

$$
\begin{aligned}
\rho_{kihjm} &= P(G_{k'jm}) \\
&= P(A_A)P(\alpha_j \mid A_A)P(S_A \mid A_A \wedge \alpha_j)P(\sigma_m \mid A_A \wedge \alpha_j \wedge S_A) \\
&+ P(A_A)P(\alpha_j \mid A_A)P(S_P \mid A_A \wedge \alpha_j)P(\sigma_m \mid A_A \wedge \alpha_j \wedge S_P) \\
&+ P(A_P)P(\alpha_j \mid A_P)P(S_A \mid A_P \wedge \alpha_j)P(\sigma_m \mid A_P \wedge \alpha_j \wedge S_A) \\
&+ P(A_P)P(\alpha_j \mid A_P)P(S_P \mid A_P \wedge \alpha_j)P(\sigma_m \mid A_P \wedge \alpha_j \wedge S_P) \qquad \ldots (8)
\end{aligned}
$$

Here, S_P is the event "partner selection is made proportionally by sexual activity class". (Note that the additive terms in the second equality correspond in order to groups i to iv in Section 2.4.)

To check the effect of choosing sexual activity class before partner's age group (and thus to check whether Condition 1 is met), we reversed the order of factors in equation 7 to obtain

$$\rho_{kihjm} = P(G_{k'jm})$$

$$= \left(\varepsilon^{(S)}\delta_{hm} + (1-\varepsilon^{(S)}) \frac{\sum_{\alpha=1}^{n_A} P_{k'\alpha m}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S} P_{k'\alpha\beta}} \right) \left(\varepsilon^{(A)}\delta_{ij} + (1-\varepsilon^{(A)}) \frac{P_{k'jm}}{\sum_{\alpha=1}^{n_A} P_{k'\alpha m}} \right)$$

$$= P(S_A)P(\sigma_m \mid S_A)P(A_A \mid S_A \wedge \sigma_m)P(\alpha_j \mid S_A \wedge \sigma_m \wedge A_A)$$

$$+ P(S_A)P(\sigma_m \mid S_A)P(A_P \mid S_A \wedge \sigma_m)P(\alpha_j \mid S_A \wedge \sigma_m \wedge A_P)$$

$$+ P(S_P)P(\sigma_m \mid S_P)P(A_A \mid S_P \wedge \sigma_m)P(\alpha_j \mid S_P \wedge \sigma_m \wedge A_A)$$

$$+ P(S_P)P(\sigma_m \mid S_P)P(A_P \mid S_P \wedge \sigma_m)P(\alpha_j \mid S_P \wedge \sigma_m \wedge A_P) \qquad \ldots (9)$$

A simple numerical substitution shows that equations 7 and 9 do not result in the same probability, and therefore cannot satisfy Condition 1 if Assumption 1 is true. For example, suppose there is a population with two age groups and two sexual activity groups with $\varepsilon^{(A)}$ = 0.3, $\varepsilon^{(S)}$ = 0.7, and $P_{k'11}$ = 40, $P_{k'12}$ = 25, $P_{k'21}$ = 20 and $P_{k'22}$ = 15. Then by equation 7 ρ_{k1111}=0.56625, but by equation 9 ρ_{k1111}=0.56733 – thus the two mixing matrix forms are not equivalent.

As the mixing matrix itself represents only one step in a simulation of sexually transmitted infections in a population over time, it is impractical to estimate *a priori* the magnitude or direction of the effect of using differing mixing matrices. While in this example this difference between the two mixing matrix entries is small (with a 0.2% higher value under equation 9), in practice such a difference can potentially have a sizable cumulative effect after numerous iterations of the mixing matrix on a population over time, as required in population modelling (for example, we routinely model population HPV transmission and natural history, simulating yearly iterations of sexual interaction and consequential HPV infection over several decades).

The mismatch cannot be corrected by assigning to $\varepsilon^{(A)}$ and $\varepsilon^{(S)}$ different values depending on whether a partner's age or sexual activity class is chosen first. In the example in the previous paragraph there are 16 matrix entries to be matched by adjusting only the two parameters $\varepsilon^{(A)}$ and $\varepsilon^{(S)}$. This is in general impossible – only two entries can be set to arbitrary values using two parameters. In practice, a mixing matrix can contain thousands of entries.

Equation 7 rewritten in the form of equation 8 immediately suggests the potential for age-dependence of $\varepsilon^{(S)}$ (i.e. $P(S_A)$), whereas equation 9 suggests the opposite, that $\varepsilon^{(A)}$ is dependent on sexual activity class selection. This clearly contradicts Assumption 1. Thus, Assumption 1 and Condition 1 cannot hold simultaneously in the mixing matrix shown in equation 7.

3. A revised mixing matrix combining assortative and proportional mixing with multiple selection criteria that is consistent with Assumptions 1 and 2 and Condition 1

We propose a revision to the mixing matrix shown in equation 7 that is consistent with Assumptions 1 and 2 and Condition 1.

3.1 Assumption 1

The following mixing matrix is consistent with the requirement that constant parameters $\varepsilon^{(A)}$ and $\varepsilon^{(S)}$ are independent of partner's age and sexual activity level (Assumption 1):

$$\rho_{kihjm} = P(G_{k'jm})$$

$$= P(A_A \wedge S_A)P(G_{k'jm} \mid A_A \wedge S_A)$$

$$+ P(A_A \wedge S_P)P(G_{k'jm} \mid A_A \wedge S_P)$$

$$+ P(A_P \wedge S_A)P(G_{k'jm} \mid A_P \wedge S_A)$$

$$+P(A_P \wedge S_P)P(G_{k'jm} \mid A_P \wedge S_P) \qquad \ldots (10)$$

In this form, assortative versus proportional selection by age group and sexual activity class is chosen before age group and sexual activity class, thus removing the population sub-group dependencies which cause the inconsistency between equations 7 and 9 in the unrevised mixing matrix.

3.2 Assumption 2

Under Assumption 2, the events A_A and S_A (partner age and sexual activity level chosen assortatively) are independent of each other. With this assumption, the terms for $P(A \wedge S)$ take the following forms:

$$P(A_A \wedge S_A) = P(A_A)P(S_A) = \varepsilon^{(A)}\varepsilon^{(S)}$$

$$P(A_A \wedge S_P) = P(A_A)P(S_P) = \varepsilon^{(A)}(1-\varepsilon^{(S)})$$

$$P(A_P \wedge S_A) = P(A_P)P(S_A) = (1-\varepsilon^{(A)})\varepsilon^{(S)}$$

$$P(A_P \wedge S_P) = P(A_P)P(S_P) = (1-\varepsilon^{(A)})(1-\varepsilon^{(S)}) \qquad \ldots (11)$$

3.3 A revised mixing matrix

Consider the forms of the various $P(G_{k'jm} \mid A \wedge S)$ terms in equation 10. When an individual's choices are assortative both by age and sexual activity, they will by definition only consider someone from the opposite sex in the same age group and sexual activity class. In this case, the probability of choosing age group *j* and sexual activity class *m* is 1 if *i* = *j* and *h* = *m*, and 0 otherwise, i.e.

$$P(G_{k'jm} \mid A_A \wedge S_A) = \delta_{ij}\delta_{hm} \qquad \ldots (12)$$

When a person's partner choice is assortative by age and proportional by sexual activity, they are open to partnerships with anyone of any sexual activity level but only within their own age group. The number of partnerships open to them is thus

$$\sum_{\beta=1}^{n_S} P_{k'j\beta} = \sum_{\beta=1}^{n_S} N_{k'j\beta} c_{k'j\beta}$$

and the probability of choosing a partner in age group *j* and sexual activity class *m* is therefore

$$P(G_{k'jm} \mid A_A \wedge S_P) = \frac{P_{k'jm}}{\sum_{\beta=1}^{n_S} P_{k'j\beta}} \delta_{ij}$$

$$= \frac{N_{k'jm} c_{k'jm}}{\sum_{\beta=1}^{n_S} N_{k'j\beta} c_{k'j\beta}} \delta_{ij} \quad \ldots (13)$$

where $N_{k'jm}$ is the number of people of sex *k'* in age group *j* and sexual activity class *m* and $c_{k'jm}$ is the average number of partnerships offered by people in this group.

Similarly, when choices are proportional by age and assortative by sexual activity, the available partnerships are within the same sexual activity class but spread across all age groups. Thus the sum in the denominator is over age groups rather than sexual activity classes, and so

$$P(G_{k'jm} \mid A_P \wedge S_A) = \frac{P_{k'jm}}{\sum_{\alpha=1}^{n_A} P_{k'\alpha m}} \delta_{hm}$$

$$= \frac{N_{k'jm} c_{k'jm}}{\sum_{\alpha=1}^{n_A} N_{k'\alpha m} c_{k'\alpha m}} \delta_{hm} \quad \ldots (14)$$

Finally, when an individual's partner choice is proportional by both age and sexual activity group, all partnerships are included in their target population. In this case,

$$P(G_{k'jm} \mid A_P \wedge S_P) = \frac{P_{k'jm}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S} P_{k'\alpha\beta}}$$

$$= \frac{N_{k'jm} c_{k'jm}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S} N_{k'\alpha\beta} c_{k'\alpha\beta}} \qquad \ldots (15)$$

Substituting equations 11-15 into equation 10 gives the complete, **revised mixing matrix**:

$$\rho_{kihjm} = \varepsilon^{(A)}\varepsilon^{(S)}\delta_{ij}\delta_{hm}$$

$$+ \varepsilon^{(A)}(1-\varepsilon^{(S)})\frac{P_{k'jm}}{\sum_{\beta=1}^{n_S} P_{k'j\beta}}\delta_{ij}$$

$$+ (1-\varepsilon^{(A)})\varepsilon^{(S)}\frac{P_{k'jm}}{\sum_{\alpha=1}^{n_A} P_{k'\alpha m}}\delta_{hm}$$

$$+ (1-\varepsilon^{(A)})(1-\varepsilon^{(S)})\frac{P_{k'jm}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S} P_{k'\alpha\beta}} \qquad \ldots (16)$$

3.4 Differences between the unrevised and revised matrices

If the unrevised mixing matrix (equation 7) is expanded, it almost matches the revised mixing matrix (equation 16). However, the following age-proportional, sexual-activity-assortative term in equation 7 prevents it from matching equation 16:

$$(1-\varepsilon^{(A)})\varepsilon^{(S)}\frac{\sum_{\beta=1}^{n_S} P_{k'j\beta}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S} P_{k'\alpha\beta}}\delta_{hm} .$$

This is because the sum of partnerships over sexual activity classes does not necessarily cancel (i.e. the ratio of partnerships offered by each sexual activity class does not necessarily remain constant across age cohorts), and so this does not match the corresponding term in equation 16.

Therefore, equation 16 is a correction to the mixing matrix first described in equation 7. Equation 16 is consistent with Assumptions 1 and 2, and it also meets Condition 1, as the partner's age group and sexual activity class are in effect chosen simultaneously, after the method of choosing a partner (i.e. assortative vs. random for age and sexual activity) has been selected.

3.5 The revised matrix applied to semi-assortative age mixing

The unrevised mixing matrix in equation 7 has been previously extended to model 'semi-assortative' mixing, in which people prefer sexual partners close to their own age. An example is a population in which partners are chosen from people within one age cohort of an individual's own age cohort, with specified probabilities for each age cohort's choices.

In order to explore this mixing structure using the revised mixing matrix, we adopt the following notation:

- $\varepsilon_{i,x}^{(A)}$: Probability that a person in age cohort i will prefer partners from age cohort $i+x$;
- d: Maximum age cohort difference for semi-assortative mixing (as opposed to proportional mixing).

The probability that someone in age cohort i chooses a partner proportionally by age is thus $1-\sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)}$.

In this case, the revised mixing matrix for a population with a mixture of semi-assortative and proportional mixing by age and assortative and proportional mixing by sexual activity class is:

$$\rho_{kihjm} = \sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)}\varepsilon^{(S)}\delta_{i+x,j}\delta_{hm}$$

$$+ \sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)}\left(1-\varepsilon^{(S)}\right)\frac{N_{k'jm}c_{k'jm}}{\sum_{\beta=1}^{n_S}N_{k'j\beta}c_{k'j\beta}}\delta_{i+x,j}$$

$$+\left(1-\sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)}\right)\varepsilon^{(S)}\frac{N_{k'jm}c_{k'jm}}{\sum_{\alpha=1}^{n_A}N_{k'\alpha m}c_{k'\alpha m}}\delta_{hm}$$

$$+\left(1-\sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)}\right)\left(1-\varepsilon^{(S)}\right)\frac{N_{k'jm}c_{k'jm}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S}N_{k'\alpha\beta}c_{k'\alpha\beta}} \qquad \ldots(17)$$

This is very similar in form to the revised mixing matrix obtained earlier (equation 16). For comparison, the unrevised matrix in equation 7 when modified to include semi-assortative age mixing takes the form:

$$\rho_{kihjm}=\left(\sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)}\delta_{i+x,j}+(1-\sum_{x=-d}^{d}\varepsilon_{i,x}^{(A)})\frac{\sum_{\beta=1}^{n_S}P_{k'j\beta}}{\sum_{\alpha=1}^{n_A}\sum_{\beta=1}^{n_S}P_{k'\alpha\beta}}\right)\left(\varepsilon^{(S)}\delta_{hm}+(1-\varepsilon^{(S)})\frac{P_{k'jm}}{\sum_{\beta=1}^{n_S}P_{k'j\beta}}\right). \qquad \ldots(18)$$

Equation 17 allows $\varepsilon_{i,x}^{(A)}$ to be independent of partner's sexual activity class and $\varepsilon^{(S)}$ to be independent of partner's age, while equation 18 does not.

In the following section, we compare how the revised mixing matrix (Equation 17) and the unrevised mixing matrix (equation 18) affect modelled estimates in practice.

4. Effect of the revised mixing matrix on a population model of HPV transmission and vaccination

For an illustration of the effect of the revised mixing matrix on the findings of a specific health policy evaluation, we used a dynamic population model of HPV transmission and vaccination in Australia, which has previously been described in detail [9, 13].

4.1 Population model structure and parameterisation

The deterministic dynamic HPV transmission model used for the current evaluation incorporated a review of Australian survey data on age-specific rates of heterosexual contacts for males and females [9, 13]. As previously described [9, 13], HPV natural history parameters were obtained by fitting the model to preliminary data on the age-specific prevalence of PCR-detected HPV DNA in cytologically normal non-Indigenous women, which was obtained from an Australian study of HPV prevalence – the "Women's HPV Indigenous Non-indigenous Urban Rural Study" (WHINURS) [14].

The dynamic HPV transmission model assumes a combination of proportional, semi-assortative and assortative mixing across sexual activity classes ('low', 'moderate', 'moderately high' and 'high') and five-year age groups. The key unknown HPV natural history parameters in males and females were adjusted to fit the observed HPV prevalence, including the age-specific duration of naturally conferred immunity, the annual rate of clearance of infection, and the per-partnership transmission probability of HPV in various sexual activity behavioural groups. Some *a priori* restrictions, which were in accordance with the existing epidemiological evidence, were placed on the range of possible parameter values and relationships between parameters [9, 13]. This "baseline" natural history parameter set was used in the current analysis of the impact of HPV vaccination.

The key outcomes that we compared for different mixing matrices were predicted HPV prevalence and the predicted effect of HPV vaccination on HPV prevalence.

4.2 Model results using the unrevised mixing matrix

The original form of the mixing matrix used by this model was the unrevised form (equation 18) with $d = 1$, based on the Garnett and Anderson formulation [1]. The predicted HPV prevalence in Australia after calibration of the model using the unrevised mixing matrix is shown in Figure 1.

4.3 Modelled results of HPV prevalence using the revised mixing matrix, without model calibration

In order to assess the effect of the revised mixing matrix on predictions of HPV prevalence, we incorporated the revised mixing matrix and re-simulated HPV transmission in the population to predict pre-vaccination HPV prevalence in females

The use of the revised mixing matrix form, when other model parameters were held constant, resulted in a maximum absolute increase in the predicted prevalence of HPV 16 infection of 0.6% in the 15-19 year old age group (a relative increase of 10%), which was the age at which the peak prevalence of infection was predicted (Figure 1). The greatest relative change was an 11% increase among women aged 25-29 years. The difference in outcomes declined with age; and over age 35 years, no substantive absolute differences in the predicted prevalence between the two simulations were observed.

4.4 Modelled results of the effect of HPV vaccination using the revised mixing matrix, with model calibration

We then assessed to what extent these differences in the predicted prevalence of HPV would change modelled predictions of the effect of HPV vaccination. To achieve this, firstly we re-calibrated the model with the revised mixing matrix in place by adjusting HPV natural history parameters (namely, rates of progression and regression of HPV infections and waning of naturally-acquired immunity), such that the predicted HPV prevalence was equivalent to that predicted when using the unrevised mixing matrix simulation. We then predicted reductions in HPV incidence following the introduction of HPV vaccination for HPV 16, HPV 16 and 18, and all oncogenic HPV infections, using previously described assumptions and methods [9], for the unrevised matrix compared to the revised matrix with adjusted parameters. For this model, we used similar vaccination coverage assumptions to those previously used [9, 13]; assuming that three-dose coverage in 12-13 year old girls was 78%. Australia's national HPV vaccination program commenced in 2007, and catch-up was performed to end-2009 for women up to the age of 26 years. Routine vaccination of 12-13 year old girls was introduced in some states in 2007, and throughout Australia in 2008. Coverage in the cohort of girls who were all vaccinated when aged 12-13 years in 2008 has not yet been reported. Coverage in the cohort of girls who were aged 12-13 years in 2007 (mostly vaccinated when aged 13-14 years in 2008; some vaccinated when aged 12-13 years in 2007) has been reported as 73% [15].

Table 2 shows the predicted age-standardised incidence of HPV (across all ages) for females and males in the year 2006 (pre-vaccination) and for the years 2010, 2020 and 2050 (3, 13 and 43 years post-vaccination) for the revised and unrevised matrices; and Table 3 shows the equivalent relative reductions in incidence, referenced to the 2006 (pre-vaccination) levels. As shown in Tables 2 and 3, after model recalibration, the mixing matrix revision did not have a substantive effect on the predicted HPV incidence reductions after vaccination.

5. Discussion

The sexual mixing matrix is a critical component of dynamic models of sexually transmitted diseases, allowing population models to reflect epidemiologic survey data on differential rates of contact between various subgroups of the population. Although splitting a mixing matrix into subgroup terms (such as age and sexual activity) is a useful abstraction, we have described two examples of such matrices (equations 3 and 7) which contained inconsistencies in their probability structures, and we have presented revised forms of both matrices (equations 4 and 16).

The revised mixing matrix presented in equation 16 has general application for dynamic models of infection in which it is important to simulate population heterogeneity in mixing, whether through sexual contact or other pathways of disease transmission that can be modelled based on the characteristics of subgroups. The degree to which the mixing matrix revision would influence the findings of a specific evaluation is likely to depend on a number of factors, including the level of heterogeneity in subgroup mixing, the calibration procedure and calibration targets, the degree to which other model parameters are adjusted to account for the revision, the degree of dependence in conditional probabilities and the particular model output of interest.

To assess whether the reformulation of the mixing matrix might have potential consequences for policy decisions based on model predictions, we tested the effects using a previously described model of HPV transmission and vaccination. We showed that, in the absence of changes to other model assumptions, revision of the mixing matrix did result in some change to the model-predicted age-specific pattern of HPV infection. This finding has important implications for modelled evaluations in which the output of interest is related to population infection rates.

A number of versions of the sexual mixing matrices discussed here have been used in published HPV cost-effectiveness studies. Of those that use the unrevised mixing matrices identified in this paper, some report HPV prevalence by age [7, 11, 16] and we have shown here that this can vary with even slight changes to the mixing matrix, and have a flow-on effect to other model estimates: in the example shown here, final estimates of relative vaccine effectiveness were substantially affected by corrections to the mixing matrix.

An additional issue is that some groups who have used unrevised mixing matrices have estimated posterior natural history parameters after model fitting [7, 10, 16]. These parameters include the per-partner transmission probability (which may vary by sex, age and sexual activity group depending on model complexity) [7, 10, 16] and the rate of infection clearance (which may vary by sex and age) [7]. These estimates may require review, using the revised mixing matrix. This is important because these natural history parameters may be adopted by other modelling groups as baseline parameters, as has been done in past For example, the estimate for the probability of HPV transmission per sexual partnership where one partner is HPV positive (60%) used by us [9] and others [17] was derived from earlier population modelling using the unrevised mixing matrix [10].

We recently revised our own estimates for HPV natural history parameters in an updated estimate of the effects of HPV vaccination of females and males in Australia, accounting for the mixing matrix revision [13]. To identify suitable sets of HPV natural history parameters we rejected sets which produced age-specific prevalence estimates in females outside the 95% confidence intervals estimated using observed data; retained parameter sets were then used to estimate a feasible range for the corresponding age-specific male HPV 16 pre-vaccination prevalence for heterosexually transmitted HPV [13].

Dynamic transmission models of HPV infection have played a key role in underpinning the introduction of prophylactic HPV vaccination in most developed countries [18]. HPV vaccination of adolescent females is consistently found to be cost-effective in the large majority of modelled evaluations [18-20]. The determination of the cost-effectiveness of HPV vaccination is based on an assessment of vaccination effectiveness in increasing the average quality-adjusted life-years in the population; for HPV vaccination this is driven by substantial predicted reductions in the future burden of cervical cancer [21, 22]. A number of evaluations have also included other outcomes, including a predicted reduction in HPV-related anogenital cancers at other sites in both females and males, and a reduction in anogenital warts [23-25]. However, the predicted benefits in all these health outcomes are underpinned by estimates of the vaccine-associated reductions in HPV infections. Therefore, model-predicted relative reductions in HPV incidence after vaccination have critical policy implications.

In the current study, we have shown that unobservable natural history parameters can be adjusted to compensate for the effects of the mixing matrix revision, and that the resulting model predicts similar outcomes for vaccine-associated relative reductions in incidence when compared to models using unrevised forms of the mixing matrix. This implies that provided that models are well-calibrated to local infection rates, previous findings that HPV vaccination of young females is cost-effective (in most settings) are likely to be robust to the revision presented here.

In conclusion, we have identified an inconsistency in previously used factorised forms of sexual mixing matrices. These mixing matrices are an important construct in population models of the spread (and prevention) of sexually-transmitted infections. We have described revised forms of these matrices, and shown that the revision has implications for modelled estimates of disease prevalence. These findings also have implications for the accurate estimation of unobservable natural history parameters for sexually transmitted infections, which can have a substantial influence on model results. However, we found that after appropriate model recalibration, important policy-relevant outcomes such as the predicted effect of vaccination may not be substantially changed by the incorporation of the revised mixing matrix. Our revised mixing matrix offers a rigorous alternative to commonly used mixing matrices that can be used to reliably and explicitly accommodate conditional probabilities, with appropriate re-calibration of unobservable model parameters.

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Table 1. Notation.

Partner preference: A_A : Partner preference is made assortatively by age A_P : Partner preference is made proportionally by age S_A : Partner preference is made assortatively by sexual activity S_P : Partner preference is made proportionally by sexual activity $\alpha_{k'j}$: A partner of sex *k'* is selected from age group *j* $\sigma_{k'm}$: A partner of sex *k'* is selected from sexual activity class *m* $G_{k'jm}$: A partner of sex *k'* is selected from age group *j* and sexual activity class *m*
Population numbers for people of sex *k'* in age group *j* and sexual activity class *m*: $N_{k'jm}$: Number of people in this group $c_{k'jm}$: Average number of partnerships offered by people in this group $P_{k'jm}$: Total number of partnerships offered by people in this group
Numbers of groups: n_A : Number of age groups n_S : Number of sexual activity classes
Assortative mixing proportions: $\varepsilon^{(A)}$: Proportion of individuals who prefer partners assortatively by age $\varepsilon^{(S)}$: Proportion of individuals who prefer partners assortatively by sexual activity class

Table 2. Predicted age-standardised HPV incidence after vaccination (using Australian 2001 population)

(a) Using the unrevised mixing matrix (equation 18)

	HPV Incidence in Females			HPV Incidence in Males		
Year	**HPV16**	**HPV16/18**	**All HPV**	**HPV16**	**HPV16/18**	**All HPV**
2006	1.4%	1.8%	6.0%	1.4%	1.8%	6.1%
2010	0.8%	1.0%	5.2%	1.0%	1.3%	5.3%
2020	0.5%	0.7%	4.9%	0.8%	1.0%	5.0%
2050	0.2%	0.3%	4.5%	0.4%	0.6%	5%

(b) Using the revised mixing matrix (equation 17) with a re-calibrated model

	HPV Incidence in Females			HPV Incidence in Males		
Year	**HPV16**	**HPV16/18**	**All HPV**	**HPV16**	**HPV16/18**	**All HPV**
2006	1.5%	1.9%	6.5%	1.4%	1.9%	6.4%
2010	0.8%	1.1%	5.6%	1.0%	1.3%	5.5%
2020	0.5%	0.7%	5.2%	0.8%	1.0%	5.1%
2050	0.2%	0.3%	4.8%	0.5%	0.6%	5%

Table 3. Predicted relative reductions in age-standardised HPV incidence after vaccination (using Australian 2001 population)

(a) Using the unrevised mixing matrix (equation 18)

	Reduction in HPV Incidence in Females			Reduction in HPV Incidence in Males		
Year	**HPV16**	**HPV16/18**	**All HPV**	**HPV16**	**HPV16/18**	**All HPV**
2010	42.5%	42.5%	12.8%	30.2%	30.2%	12.5%
2020	63.4%	63.4%	19.0%	44.9%	44.9%	18.7%
2050	86.0%	86.0%	25.8%	68.2%	68.2%	25.4%

(b) Using the revised mixing matrix (equation 17) with a re-calibrated model

	Reduction in HPV Incidence in Females			Reduction in HPV Incidence in Males		
Year	**HPV16**	**HPV16/18**	**All HPV**	**HPV16**	**HPV16/18**	**All HPV**
2010	42.6%	42.6%	12.8%	32.3%	32.3%	13.0%
2020	62.9%	62.9%	18.9%	45.9%	45.9%	19.2%
2050	85.4%	85.4%	25.6%	68.2%	68.2%	26.0%