Supplementary Material

Estimating the syphilis epidemic among gay, bisexual and other men who have sex with men in Australia following changes in HIV care and prevention

Anna L. Wilkinson\textsuperscript{A,B,*}, Nick Scott\textsuperscript{A,B,*}, Tom Tidhar\textsuperscript{A}, Phillip Luong\textsuperscript{A}, Carol El-Hayek\textsuperscript{A}, David P. Wilson\textsuperscript{A}, Christopher K. Fairley\textsuperscript{C,D}, Lei Zhang\textsuperscript{C,D}, David Leslie\textsuperscript{E,†}, Norman Roth\textsuperscript{F}, B. K. Tee\textsuperscript{G}, Margaret Hellard\textsuperscript{A,B,H} and Mark Stoové\textsuperscript{A,B,I}

\textsuperscript{A}Disease Elimination Program, Burnet Institute, 85 Commercial Road, Melbourne, Vic. 3004, Australia.
\textsuperscript{B}School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Commercial Road, Melbourne, Vic. 3004, Australia.
\textsuperscript{C}Melbourne Sexual Health Centre, Alfred Health, 580 Swanston Street, Carlton, Vic. 3053, Australia.
\textsuperscript{D}Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Commercial Road, Melbourne, Vic. 3004, Australia.
\textsuperscript{E}Victorian Infectious Disease Laboratory, 792 Elizabeth Street, Melbourne, Vic. 3000, Australia.
\textsuperscript{F}Prahran Market Clinic, Pran Central, Mezzanine Level, corner Commercial Road and Chapel Street, Prahran, Vic. 3181, Australia.
\textsuperscript{G}The Centre Clinic, 77 Fitzroy Street, St Kilda, Vic. 3182, Australia.
\textsuperscript{H}Infectious Disease Department, Alfred Health, Alfred Hospital, Commercial Road, Melbourne, Vic. 3004, Australia.
\textsuperscript{I}Corresponding author. Email: mark.stoove@burnet.edu.au

\textsuperscript{*}Authors A. L. Wilkinson and N. Scott contributed equally to this manuscript.

\textsuperscript{†}Deceased.
<table>
<thead>
<tr>
<th>Table S1. Model parameters</th>
<th>Value</th>
<th>Symbol</th>
<th>Source/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effectiveness of condoms at preventing HIV/syphilis</td>
<td>70%</td>
<td>$\epsilon_c$</td>
<td>(1)</td>
</tr>
<tr>
<td>Effectiveness of PrEP at preventing HIV</td>
<td>86%</td>
<td>$\delta_p$</td>
<td>(2)</td>
</tr>
<tr>
<td>Reduction in HIV infectiousness when virally suppressed</td>
<td>96%</td>
<td>$\delta$</td>
<td>(3)</td>
</tr>
<tr>
<td><strong>Syphilis parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of exposed stage (days)</td>
<td>21</td>
<td>$1/\beta_1$</td>
<td>(4, 5)</td>
</tr>
<tr>
<td>Duration of infectious stage (days)</td>
<td>730.5 (1-3 years)</td>
<td>$1/\beta_2$</td>
<td>(4, 5)</td>
</tr>
<tr>
<td>Duration of treatment from late latent stage</td>
<td>7</td>
<td>$1/\beta_3$</td>
<td>(4)</td>
</tr>
<tr>
<td>Proportion of GBM at high-risk of syphilis</td>
<td>18%</td>
<td>$\gamma$</td>
<td>(6)$^+$</td>
</tr>
<tr>
<td>Increased syphilis risk for high-risk GBM</td>
<td>9.68</td>
<td>$\Gamma$</td>
<td>(6)$^+$</td>
</tr>
<tr>
<td>Proportion who test frequently</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative GBM</td>
<td>69%</td>
<td>$\omega^-$</td>
<td>The Burnet Institute$^*$</td>
</tr>
<tr>
<td>HIV-positive GBM</td>
<td>90%</td>
<td>$\omega^+$</td>
<td></td>
</tr>
<tr>
<td><strong>Syphilis testing frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative GBM</td>
<td>1/224 days</td>
<td>$\tau^-$</td>
<td>VPCNSS</td>
</tr>
<tr>
<td>HIV-positive GBM</td>
<td>1/133 days</td>
<td>$\tau^+$</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual risk parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of serodiscordant sex acts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-positive GBM</td>
<td>5%</td>
<td>$\alpha^+$</td>
<td>(7)</td>
</tr>
<tr>
<td>HIV-negative GBM (no PrEP)</td>
<td>5%</td>
<td>$\alpha^-$</td>
<td>(7)</td>
</tr>
<tr>
<td>HIV-negative GBM (PrEP)</td>
<td>5%</td>
<td>$\alpha^-$</td>
<td>Assumed</td>
</tr>
<tr>
<td>Condom use with casual partners</td>
<td>42%</td>
<td>$c$</td>
<td>(8)</td>
</tr>
<tr>
<td>Average time at risk of sexually transmitted infections</td>
<td>50 years</td>
<td>$1/\mu$</td>
<td>Assumed 15-64 year olds</td>
</tr>
</tbody>
</table>

$^*$Syphilis monitoring report, November 2015, Burnet Institute, includes unpublished data from the Victorian Primary Care Network on Sentinel Surveillance (VPCNSS) and the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance projects.

$^+$PrEP trial data in Australia found that 18% of participants accounted for 68% of STI infections. (6) The increased risk was calculated as: ([68/18] infections per person at high risk) / ([32/82] infections per person for low risk) = 9.68.
<table>
<thead>
<tr>
<th>Year</th>
<th>Victorian population size*</th>
<th>Victorian GBM population size†</th>
<th>Victorian HIV+ GBM population size‡</th>
<th>Victorian HIV notifications$</th>
<th>Victorian syphilis notifications as of July 2018‖</th>
<th>Victorian notified infectious syphilis among GBMΔ</th>
<th>Among HIV+ GBMΔ</th>
<th>Among HIV-GBM◊</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5,445,172</td>
<td>49447</td>
<td>3560</td>
<td>178</td>
<td>291</td>
<td>189</td>
<td>42</td>
<td>148</td>
</tr>
<tr>
<td>2011</td>
<td>5,520,378</td>
<td>51919</td>
<td>3738</td>
<td>218</td>
<td>322</td>
<td>209</td>
<td>46</td>
<td>163</td>
</tr>
<tr>
<td>2012</td>
<td>5,611,981</td>
<td>54515</td>
<td>3925</td>
<td>200</td>
<td>467</td>
<td>304</td>
<td>67</td>
<td>237</td>
</tr>
<tr>
<td>2013</td>
<td>5,710,847</td>
<td>57241</td>
<td>4121</td>
<td>218</td>
<td>654</td>
<td>467</td>
<td>103</td>
<td>364</td>
</tr>
<tr>
<td>2014</td>
<td>5,817,241</td>
<td>60103</td>
<td>4327</td>
<td>219</td>
<td>632</td>
<td>411</td>
<td>90</td>
<td>321</td>
</tr>
<tr>
<td>2015</td>
<td>5,924,297</td>
<td>63108</td>
<td>4544</td>
<td>206</td>
<td>949</td>
<td>617</td>
<td>136</td>
<td>482</td>
</tr>
<tr>
<td>2016</td>
<td>6,036,731</td>
<td>66263</td>
<td>4771</td>
<td>233</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>6,143,715</td>
<td>69577</td>
<td>5010</td>
<td>194</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>6,252,595</td>
<td>73055</td>
<td>5260</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Australian Bureau of Statistics 2006–2016 (9)
† Estimated to be 42,000 in Victoria in 2006 (10), assuming annual growth rate of 5%
‡ Calculated based on estimated HIV prevalence among GBM (11)
§ Kirby Institute 2017: annual surveillance report (12)
‖ Victorian Department of Health and Human Services syphilis notification data, by demographic and risk factor (88% of notifications are male; 74% of male notifications were GBM) (13)
Δ Victorian Department of Health and Human Services syphilis notification data: 25% of notifications were among people living with HIV, and 88% of these were GBM (13)
◊ Remaining syphilis notifications among GBM after subtracting HIV-positive GBM syphilis notifications
Figure S1: HIV-model calibration. Panels show the HIV notifications over time (top-left); the number of people living with HIV (top-right); the prevalence of HIV (bottom-left); and the care cascade of HIV (bottom-right).
Model equations

1. Define the following compartments and stratifications

\[ t = \text{time (implemented in monthly time steps)} \]
\[ P(t) = \text{total estimated GBM population size} \]
\[ P^+(t), P^-(t), P^-\text{ are total model population size for HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM respectively. Note that these are functions of time due to population growth.} \]
\[ S^+(t), S^-(t), S^-\text{ are total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) susceptible for syphilis compartments} \]
\[ E^+(t), E^-(t), E^-\text{ are total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) exposed to syphilis compartments} \]
\[ I^+(t), I^-(t), I^-\text{ are total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) infectious with syphilis compartments} \]
\[ L^+(t), L^-(t), L^-\text{ are total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) late latently syphilis compartments} \]
\[ T^+(t), T^-(t), T^-\text{ are total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) treatment compartments} \]

\[ i = \text{subscript to indicate whether or not someone is at low or high risk of syphilis (i=0 for low and i=1 for high).} \]

2. Define the following parameters

\[ \beta_1 = \frac{1}{\text{average duration of syphilis exposed period (21 days)}} \]
\[ \beta_2 = \frac{1}{\text{average duration of syphilis infectious stage (730 days)}} \]
\[ \beta_3 = \frac{1}{\text{syphilis treatment duration (7 days)}} \]
\[ \omega^+, \omega^-, \omega^-\text{ are fraction of HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM who test regularly for syphilis} \]
\[ \tau_i^+, \tau_i^-, \tau_i^- = \frac{1}{\text{average time between tests for HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM. Note that these are equal to zero for the fraction who do not regularly test for syphilis.}} \]
\[ \gamma^+, \gamma^-, \gamma^-\text{ are fraction of HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM who are at high risk for syphilis} \]
\[ \delta = \text{relative reduction in the risk of HIV infection for people with viral suppression} \]
\[ \delta_\text{PrEP} = \text{relative reduction in the risk of HIV infection for people on PrEP} \]
\[ D(t) = \text{fraction of people with HIV who are virally suppressed} \]
\[ \mu = \frac{1}{\text{average time at risk (assumed to be 50 years; 15-64 year olds)}} \]
\[ \alpha^+, \alpha^-, \alpha^-\text{ are the proportion of sex acts undertaken by HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) populations that are serodiscordant (5%, 5% and 10% respectively)} \]
\[ \Gamma_i = \text{additional risk factor for GBM at high risk of syphilis. Note that } \Gamma_i = 1 \text{ if } i=0 \text{ (low risk is the reference)} \]
\[ c^+, c^-, c^-\text{ are average condom use among HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM.} \]
\[ \epsilon_c = \text{effectiveness of condoms} \]

3. Force of infection

Let \( \lambda_{HIV} \) be the proportionality constant (determined in the calibration procedure) for the force of HIV infection. Then the force of infection for HIV among non-PrEP (\( \Theta^- \)) and PrEP (\( \Theta^-\text{PrEP} \)) users is given by:
$$\Theta^- = \lambda_{HIV}(1 - \epsilon_c e^-) \frac{[(1 - \delta)D(t) + (1 - D(t))]P^+}{P^+ + P^- + P^0}$$

$$\Theta^+ = \lambda_{HIV}(1 - \epsilon_c e^+) \frac{[(1 - \delta)D(t) + (1 - D(t))]P^+}{P^+ + P^- + P^0}$$

Let $\lambda^+, \lambda^-, \lambda^-$ be the proportionality constants (determined in the calibration procedure) for the force of syphilis infection among HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM respectively. The force of infection for syphilis among these populations was modelled to account for condom use and mixing between HIV-positive and HIV-negative GBM populations:

$$\Phi^+_i = \lambda^+ \Gamma_i(1 - \epsilon_c c^+ \left(\frac{I^-}{p^- + p^-} + (1 - \alpha^+) \frac{I^+}{p^+}\right))$$

$$\Phi^-_i = \lambda^- \Gamma_i(1 - \epsilon_c c^- \left(\frac{1 - I^-}{p^- + p^-} + \alpha^- \frac{I^+}{p^+}\right))$$

$$\Phi^-_i = \lambda^- \Gamma_i(1 - \epsilon_c c^- \left(1 - \frac{I^-}{p^- + p^-} + \alpha^- \frac{I^+}{p^+}\right))$$

4. HIV-positive GBM differential equations

$$\frac{dS^+_i}{dt} = \Theta^- S^-_i + \Theta^-(1 - \delta \rho)S^-_i - \Phi^+_i S^+_i + \beta_2 T^+_i - \mu S^+_i$$

$$\frac{dE^+_i}{dt} = \Theta^- E^-_i + \Theta^-(1 - \delta \rho)E^-_i + \Phi^+_i S^+_i - \beta_1 E^+_i - \tau^+_i \omega^+ E^+_i - \mu E^+_i$$

$$\frac{dI^+_i}{dt} = \Theta^- I^-_i + \Theta^-(1 - \delta \rho)I^-_i + \beta_1 E^+_i - \beta_2 I^+_i - \tau^+_i \omega^+ I^+_i - \mu I^+_i$$

$$\frac{dL^+_i}{dt} = \Theta^- L^-_i + \Theta^-(1 - \delta \rho)E^-_i + \beta_2 I^+_i - \tau^+_i \omega^+ L^+_i - \mu L^+_i$$

$$\frac{dT^+_i}{dt} = \Theta^- T^-_i + \Theta^-(1 - \delta \rho)T^-_i + \tau^+_i \omega^+ \left(E^+_i + I^+_i + L^+_i\right) - \beta_3 T^+_i - \mu T^+_i$$

5. HIV-negative (no PrEP) GBM differential equations

$$\frac{dS^-_i}{dt} = \frac{dP(t)}{dt} - \Theta^- S^-_i - \Phi^-_i S^-_i + \beta_2 T^-_i - \mu S^-_i$$

$$\frac{dE^-_i}{dt} = -\Theta^- E^-_i + \Phi^-_i S^-_i - \beta_1 E^-_i - \tau^-_i \omega^- E^-_i - \mu E^-_i$$

$$\frac{dI^-_i}{dt} = -\Theta^- I^-_i + \beta_1 E^-_i - \beta_2 I^-_i - \tau^-_i \omega^- I^-_i - \mu I^-_i$$

$$\frac{dL^-_i}{dt} = -\Theta^- L^-_i + \beta_2 I^-_i - \tau^-_i \omega^- L^-_i - \mu L^-_i$$

$$\frac{dT^-_i}{dt} = -\Theta^- T^-_i + \tau^-_i \omega^- \left(E^-_i + I^-_i + L^-_i\right) - \beta_3 T^-_i - \mu T^-_i$$
6. HIV-negative (PrEP) GBM differential equations

\[ \frac{dS_i^c}{dt} = -\theta^c (1 - \delta_p^c)S_i^c - \Phi_1^c S_i^c - \beta_3 T_i^c - \mu S_i^c \]

\[ \frac{dE_i^c}{dt} = -\theta^c (1 - \delta_p^c)E_i^c + \Phi_1^c S_i^c - \beta_1 E_i^c - \tau_i^c \omega^c E_i^c - \mu E_i^c \]

\[ \frac{dT_i^c}{dt} = -\theta^c (1 - \delta_p^c)T_i^c + \beta_1 E_i^c - \beta_2 T_i^c - \tau_i^c \omega^c T_i^c - \mu T_i^c \]

\[ \frac{dL_i^c}{dt} = -\theta^c (1 - \delta_p^c)L_i^c + \beta_2 I_i^c - \tau_i^c \omega^c L_i^c - \mu L_i^c \]

\[ \frac{dT_i^{-c}}{dt} = -\theta^c (1 - \delta_p^c)T_i^{-c} + \tau_i^c \omega^{-c} (E_i^c + I_i^c + L_i^c) - \beta_3 T_i^{-c} - \mu T_i^{-c} \]

References


