Quantifying HIV-1 transmission due to contaminated injections

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Assessments of the importance of different routes of HIV-1 (HIV) transmission are vital for prioritization of control efforts. Lack of consistent direct data and large uncertainty in the risk of HIV transmission from HIV-contaminated injections has made quantifying the proportion of transmission caused by contaminated injections in sub-Saharan Africa difficult and unavoidably subjective. Depending on the risk assumed, estimates have ranged from 2.5% to 30% or more. We present a method based on an age-structured transmission model that allows the relative contribution of HIV-contaminated injections, and other routes of HIV transmission, to be robustly estimated, both fully quantifying and substantially reducing the associated uncertainty. To do this, we adopt a Bayesian perspective, and show how prior beliefs regarding the safety of injections and the proportion of HIV incidence due to contaminated injections should, in many cases, be substantially modified in light of age-stratified incidence and injection data, resulting in improved (posterior) estimates. Applying the method to data from rural southwest Uganda, we show that the highest estimates of the proportion of incidence due to injections are reduced from 15.5% (95% credible interval) (0.7%, 44.9%) to 5.2% (0.5%, 17.0%) if random mixing is assumed, and from 14.6% (0.7%, 42.5%) to 11.8% (1.2%, 32.5%) under assortative mixing. Lower, and more widely accepted, estimates remain largely unchanged, between 1% and 3% (0.1–6.3%). Although important uncertainty remains, our analysis shows that in rural Uganda, contaminated injections are unlikely to account for a large proportion of HIV incidence. This result is likely to be generalizable to many other populations in sub-Saharan Africa.

Bayesian | HIV/AIDS | mathematical modeling | blood transfusion | vertical transmission

Although controversial, recent suggestions that HIV-1 (HIV)-contaminated (hereafter referred to as "contaminated") injections might be a major, but largely overlooked, route of HIV transmission in sub-Saharan Africa, should be considered seriously (1, 2). If true, there would be profound implications for HIV control policy in the region. Moreover, the controversy has highlighted the lack of data on the risk of HIV transmission from contaminated injections, which has made the assessment of the role of contaminated injections in HIV transmission in the region difficult, and has permitted estimates of the proportion of transmission caused by contaminated injections to range widely, from 2.5% to 30% or more (1, 3).

The widespread view that only a small proportion of HIV infections in sub-Saharan Africa are due to the reuse of injection equipment in the absense of effective sterilization (hereafter referred to as "unsafe injections") is based on the assumption that the risk of transmission from unsafe injections can be adequately estimated by using needlestick injury data (3). A recent review indicates that the transmission probability from all needlestick injuries is ≈1 in 500 contaminated injections (4). However, it has been argued that because most documented contaminated needlestick injuries represent superficial wounds and are often followed by postexposure prophylaxis, these data may substantially underestimate the risk from unsafe injections. Advocates of this position have suggested that the risk of transmission from contaminated injections might be better estimated by looking at only those needlestick injuries leading to deep wounds, giving transmission probabilities of ≈1 in 50 and resulting in a very different conclusion about the overall role of injections in HIV transmission (1). Such high estimates of transmission probabilities have, in turn, been criticized as being biologically implausible (5). Because of the difficulties in measuring the risk of transmission from contaminated injections, evaluating the competing claims remains difficult and is unavoidably subjective.

We present an approach to this problem that has the potential to reconcile these different positions. We make use of high-quality age-stratified data on HIV incidence and prevalence and injection rates from a general population cohort study in rural southwest Uganda [Fig. 1 *a–c* and supporting information (SI) *Text*]. If contaminated injections are an important route of HIV transmission, large variations in injection rates should be reflected in variations in incidence among age groups. More generally, we can estimate the relative importance of unsafe injections and other transmission routes by analyzing the age-stratified data. To do this, we developed an age-stratified model that accounts for transmission due to unsafe injections, unsafe transfusions, and mother-to-child transmission. We then parameterized the model by using data from the cohort study in southwest Uganda, observational surveys within East Africa, and a systematic literature review and meta-analysis (see Fig. 1 *a–c*, *Materials and Methods*, and *SI Text*). Because there is considerable additional uncertainty in rates of exposure for sexual transmission, we excluded this route of transmission and only used incidence data from those aged 12 and under when fitting the model.

We dealt with the lack of definitive data on the risk of HIV transmission from a contaminated injection by using a Bayesian approach, and explicitly modeled different prior beliefs about this

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Abbreviation: HIV, HIV-1.

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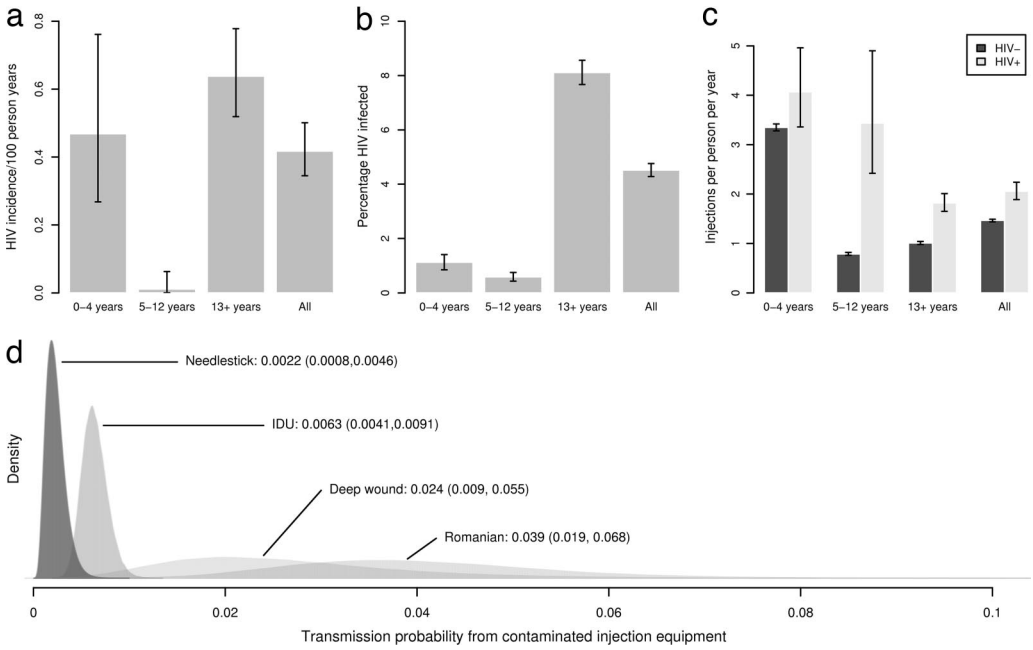

Fig. 1. Principal data and informative prior distributions used for this study. (*a*) HIV incidence by age in rural Masaka, southwest Uganda (per 100 person-years, 95% credible interval). (*b*) HIV prevalence by age in Masaka (%, 95% credible interval). (*c*) Injection rates by HIV infection status and age in Masaka (per person per year, 95% credible interval). (*d*) Informative prior distributions for the probability of transmission from contaminated unsafe injection equipment (%, *p*). The median (95% credible interval) for each distribution is shown. Priors were derived from estimates from needlestick injuries (4), injecting drug users (6), needlestick injuries causing deep wounds (1, 7, 8) and nosocomial spread in a Romanian hospital (1). The ''noninformative'' or Diffuse prior also considered (but not shown) has a median value (95% credible interval) of 50% (2.5%, 97.5%). See *SI Text* for the method of estimating mother-to-child incidence.

risk (Fig. 1*d*). These different priors reflect different beliefs about the most reliable data sources for estimating the risk of HIV transmission from a contaminated injection. This approach allows us to determine how much transmission should be attributed to each route by holders of these different beliefs, test which beliefs are consistent with the data, and evaluate whether and how these prior beliefs should be modified in light of the data.

Four informative priors representing four datasets are considered. These represent the risk of transmission estimated from (*i*) all needlestick injuries (4), (*ii*) injecting drug users (6), (*iii*) needlestick injuries resulting in deep wounds (1, 7, 8), and (*iv*) nosocomial spread in a Romanian hospital (1).

In addition to the four informative priors, we also considered a diffuse prior, corresponding to the (untenable) prior belief that the probability of transmission from a contaminated injection is equally likely to take any value between zero and one.

In the main analysis, the prior probability that injections were unsafe was derived from survey data (9), allowing for the effect that partial washing and heating of injection equipment may have in diluting or inactivating HIV. Two further analyses examine the sensitivity of the results to this choice of prior.

The mixing patterns determining the age groups of consecutive recipients of unsafe injections represent an important source of uncertainty (10). Children, for example, may be relatively more likely to visit the same clinic for immunizations as other children, and therefore may be more likely to receive unsafe injections previously used on other children than on other adults. However, reliable data are entirely lacking. Therefore we performed the analysis for two extremes: under an age-dependent (assortative) mixing assumption, we assume consecutive recipients of unsafe injections are only exposed to others in the same age group; and under a random mixing assumption, we assume that consecutive recipients are selected at random from all age groups.

Results

For all five priors, we present results from both the prior model (before confrontation with the data) and from the posterior model to show how the beliefs represented by the priors should be modified in light of the incidence data (Table 1). In all scenarios, a large proportion of all-age HIV incidence was explained by mother-to-child transmission; irrespective of the prior, median posterior estimates (range of 95% credible intervals) were ≈28% (20%, 38%). There was similar agreement about the proportion of all-age incidence explained by blood transfusions, which was ≈0.2% (0.0%, 2.0%) for all priors and posteriors.

Prior estimates of the proportion of all-age incidence attributable to injections varied widely, from ≈0.8% (0.0%, 2.9%) under the Needlestick prior, to ≈15% (0.7%, 44.9%) under the Romanian prior. Under the Diffuse prior, the model predicted an incidence due to injections alone that was greater than the total observed incidence.

Estimates of the proportion of HIV transmission due to injections under the Deep Wound, Romanian, and Diffuse priors were all modified substantially by confrontation with the data, in all cases falling to ≈5% (range of 95% credible intervals, 0.3–17.0%) under the random mixing scenario (Table 1 and Fig. 2). These declines were less marked under the age-dependent mixing scenario and the narrowing of the credible intervals was smaller. Nonetheless, support for a proportion of transmission in excess of 30% was greatly reduced; this probability fell from 0.12 and 0.03 under the Romanian and Deep Wound priors to 0.04 and 0.009 under the corresponding posteriors. In contrast, the posterior estimates under the Needlestick and Injecting Drug User scenarios (which assumed much lower transmission probabilities from contaminated injections) differed only slightly from the prior estimates, indicating their greater consistency with the HIV incidence data (range of medians, 1.0–3.0%; range of 95% credible intervals, 0.1–6.3%). The posterior probability that >30% of HIV incidence is caused by unsafe injections was ≤0.04 in all scenarios except the (untenable) Diffuse scenario.

Estimates of the probability that an injection is unsafe and the transmission probability from unsafe injections under the Deep

Table 1. Prior and posterior estimates of the percentage of total (all age) observed incidence attributable to each transmission route (median, 95% credible interval)

Model priors for the probability of transmission from contaminated injection equipment	Route of transmission and mixing assumption							
	Injections		Transfusions		Mother to child		Other	
	Random	Age-dependent	Random	Age-dependent	Random	Age-dependent	Random	Age-dependent
Needlestick								
Prior	0.8 (0.0, 2.9)	0.8 (0.0, 2.7)	0.2 (0.0, 1.5)	0.2 (0.0, 1.5)	34.2 (23.3, 47.5)	34.3 (23.3, 47.6)	64.5 (51.1, 75.5)	64.5 (51.1, 75.6)
Posterior	1.1 (0.1, 3.1)	1.0 (0.1, 3.0)	0.2 (0.0, 1.8)	0.3 (0.0, 2.0)	28.7 (20.9, 38.0)	28.9 (21.1, 38.2)	69.7 (60.3, 77.6)	69.5 (60.1, 77.4)
IDU								
Prior	2.6 (0.1, 6.4)	2.5 (0.1, 6.0)	0.2 (0.0, 1.5)	0.2 (0.0, 1.5)	34.2 (23.3, 47.5)	34.2 (23.2, 47.6)	62.7 (48.9, 74.3)	62.8 (49.1, 74.3)
Posterior	2.8 (0.3, 6.2)	3.0 (0.3, 6.3)	0.2 (0.0, 1.5)	0.2 (0.0, 1.7)	28.4 (20.7, 37.6)	28.8 (21.1, 37.9)	68.3 (58.7, 76.5)	67.8 (58.1, 76.1)
Deep wound								
Prior	9.4 (0.4, 34.1)	8.9 (0.4, 31.9)	0.2 (0.0, 1.5)	0.2 (0.0, 1.4)	34.3 (23.3, 47.6)	34.2 (23.3, 47.5)	55.1 (28.3, 71.2)	55.7 (30.3, 71.4)
Posterior	4.8 (0.5, 14.9)	8.7 (0.9, 25.4)	0.2 (0.0, 1.4)	0.2 (0.0, 1.5)	28.0 (20.2, 37.4)	28.6 (20.9, 37.8)	66.3 (54.3, 75.5)	61.9 (44.2, 73.7)
Romanian								
Prior	15.5 (0.7, 44.9)	14.6 (0.7, 42.5)	0.2 (0.0, 1.5)	0.2 (0.0, 1.5)	34.2 (23.3, 47.6)	34.2 (23.3, 47.6)	49.4 (17.7, 69.8)	50.2 (20.3, 69.9)
Posterior	5.2 (0.5, 17.0)	11.8 (1.2, 32.5)	0.2 (0.0, 1.4)	0.2 (0.0, 1.4)	28.0 (20.1, 37.3)	28.4 (20.7, 37.6)	65.8 (52.8, 75.4)	58.9 (37.6, 72.7)
Diffuse								
Prior	162 (3.2, 704)	156 (3.0, 681)	0.2 (0.0, 1.5)	0.2 (0.0, 1.5)	34.3 (23.3, 47.7)	34.3 (23.3, 47.5)	−97.6 (−639, 63.0)	−91.1 (−617, 63.5)
Posterior	4.6 (0.3, 16.4)	12.8 (1.0, 49.5)	0.2 (0.0, 1.4)	0.2 (0.0, 1.4)	28.0 (20.2, 37.3)	28.3 (20.5, 37.6)	66.3 (53.5, 75.7)	57.9 (22.0, 73.1)

Note that under the Diffuse prior, the model predicted an incidence due to injections alone that was greater than the total observed incidence. Consequently, the prior estimate of the ''Other'' incidence was negative in this scenario.

Wound, Romanian, and Diffuse priors were also modified by confrontation with the data, and became negatively correlated. This is seen most clearly under the Diffuse prior (Fig. 3, "q against p" column). In other words, in this population, beliefs that the risk of transmission from contaminated unsafe injections was high and that a high proportion of injection equipment was unsafe were not consistent with the observed age-specific HIV incidence rates.

In all posterior models, the majority of the HIV incidence observed among 0- to 4-year-olds was explained by mother-to-child transmission, a much smaller proportion was explained by unsafe injections, and a very small proportion was explained by unsafe transfusions (Fig. 4). Among 5- to 12-year-olds, in all but the Needlestick scenario with age-dependent mixing, most of the low HIV incidence observed was explained by unsafe injections. Among

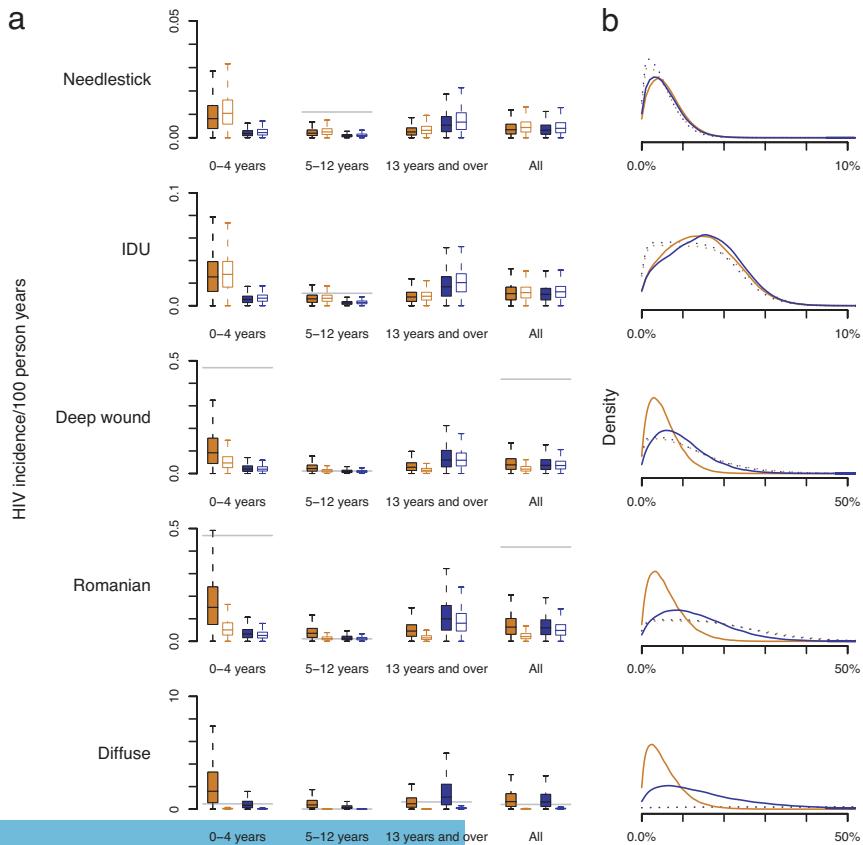

Fig. 2. HIV incidence due to unsafe injections. (*a*) Prior and posterior estimates of HIV incidence due to unsafe injections by age (boxplots show the median, lower, and upper quartiles, and the most extreme points that are no more than 1.5 times the interquartile range from the box). Solid boxes (positions 1 and 3 in each group of 4) show prior results, and open boxes show posterior results (positions 2 and 4 in each group of 4) under random mixing (red) and age-dependent (blue) mixing assumptions. Observed incidence is shown as a gray horizontal line, provided it lies within the range of the *y* axis. (*b*) Prior and posterior distributions for the proportion of observed all age incidence explained by unsafe injections. Prior (dotted lines) and posterior (solid lines) distributions are shown for random mixing (red) and age-dependent (blue) mixing of injection equipment. Note differences in axis scales.

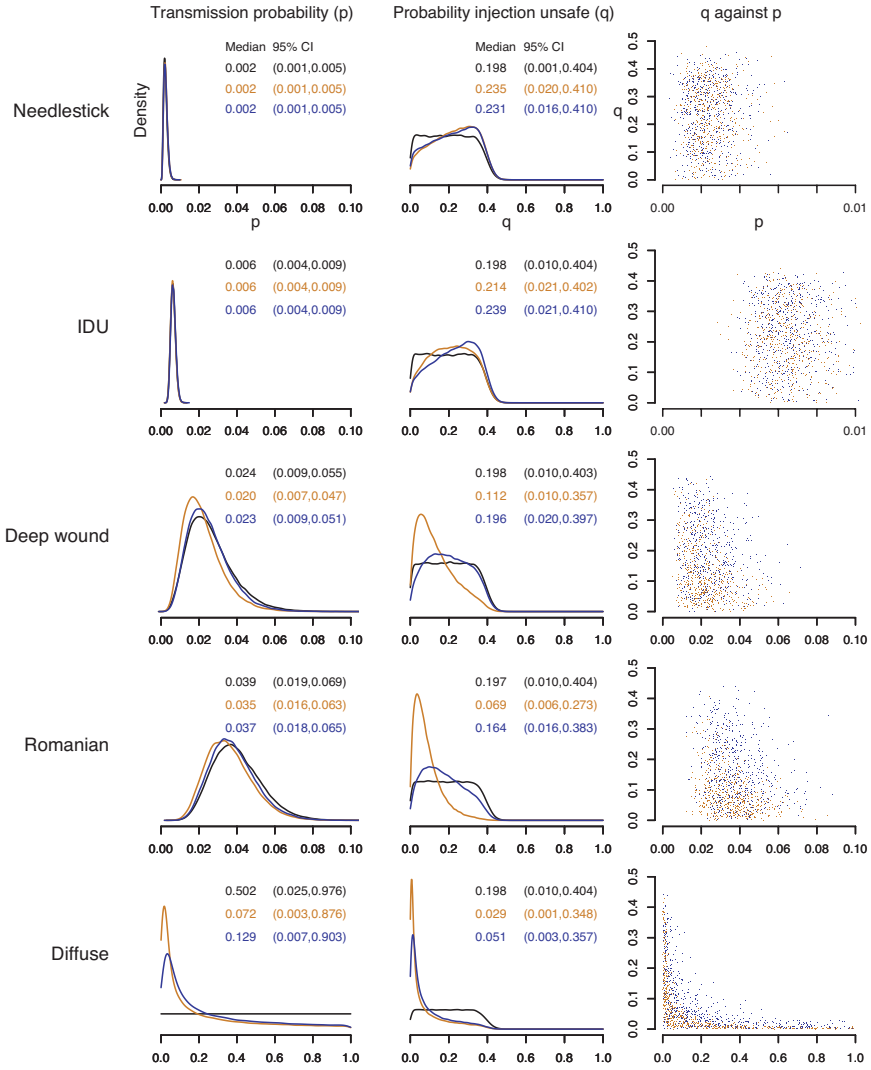

Fig. 3. Prior and posterior distributions of the transmission probability from contaminated unsafe injection equipment (p), the probability injection equipment is unsafe (q), and their correlation. Prior (black) and posterior distributions under assumed random mixing of injection equipment (red) and age-dependent mixing (blue) are shown. Medians and 95% credible intervals are shown as text. Scatter-plots of samples from the joint posterior distributions of p and q (column 3) show correlation between parameter estimates for priors with higher values of p. Note differences in axis scales.

those aged 13 years and older, the great majority of HIV incidence was left unexplained by unsafe injections, unsafe transfusions, and mother-to-child transmission, and is presumably due to sexual transmission. Over all ages, more than half of the HIV incidence was left unexplained by these three routes of transmission ("All" in Fig. 4).

A sensitivity analysis that assumed a uniform distribution for the prior probability that injections were unsafe (so all values between zero and one were equally likely) sometimes led to dramatically different priors, but broadly similar posteriors. For example, under the Deep Wound scenario, the proportion of transmission due to injections fell from 23.6% (1.1%, 83.8%) and 22.1% (1.0%, 79.0%) under random and age-dependent mixing, respectively, to 5.2% (0.5%, 17.1%) and 13.2% (1.3%, 41.0%) under the corresponding posteriors, respectively (SI Table 2). A second sensitivity analysis using a random effects model for injection safety based on data from the region, gave median estimates under the Deep Wound and Romanian scenarios approximately a factor of two lower than those in the main analysis (SI Table 3). Posterior credible intervals were, however, similar to those in the main analysis.

Discussion

Our findings suggest that, in rural Uganda, unsafe injections are very unlikely to account for a large proportion of HIV incidence. Despite an uncertain transmission probability from contaminated injections, age-stratified injection and HIV incidence data enabled us to refine estimates of the importance of unsafe injections in HIV transmission. In this study, this confrontation with data reduced the highest estimates for the proportion of incidence due to injections from 15.5% (0.7%, 44.9%) to 5.2% (0.5%, 17.0%) under random mixing and from 14.6% (0.7%, 42.5%) to 11.8% (1.2%, 32.5%) under assortative mixing. With lower, and more widely accepted, risks, no such reduction occurs and estimates remain largely unchanged, between 1% and 3% (0.1%, 6.3%). Over all ages, more than half of the HIV incidence was left unexplained by unsafe injections, unsafe transfusions, and mother-to-child transmission. Sexual transmission is the most credible explanation for this unexplained incidence because the great majority of this shortfall occurred among those aged 13 years and older, for whom sexual risk behaviors are reported (11).

Considerable and important uncertainty remains regarding the role of injections. If additional data become available, the Bayesian approach presented would allow the estimates to be updated, and the posterior estimates should converge to the true values for this population irrespective of the prior beliefs, which will have progressively less influence. Our analysis shows that surprisingly large reductions in this uncertainty could be achieved by collecting data on the mixing patterns that determine the age groups of consecutive recipients of

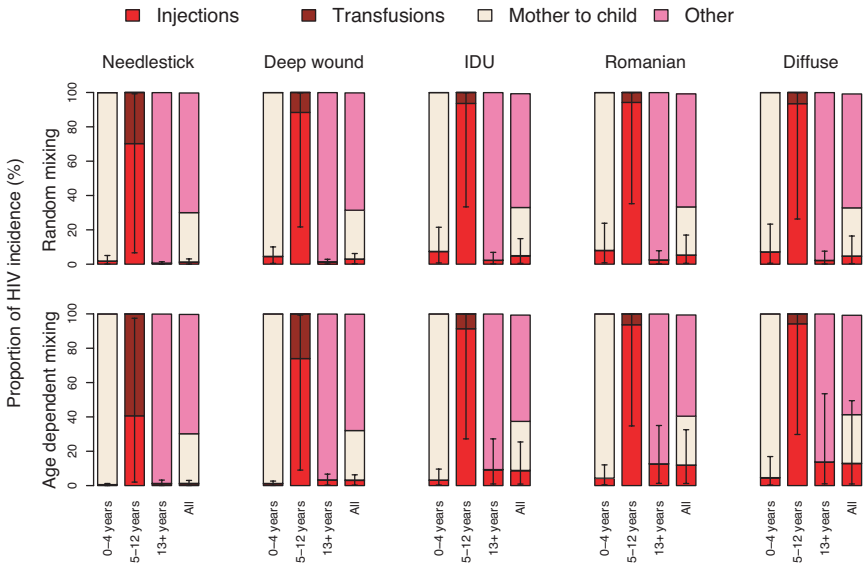

Fig. 4. Median proportion of posterior HIV incidence (%) attributable to each route of transmission, by age group. Error bars indicate 95% credible intervals for proportion of incidence due to unsafe injections.

injections (Table 1). A smaller increase in precision could also be obtained if injection safety was known with more certainty. For example, the 95% credible interval for the posterior proportion of HIV incidence attributed to injections under the Deep Wound prior and age-dependent mixing was 1–25%, but it narrowed to 4–21% if the proportion of injections that were unsafe was known to be exactly 20% (SI Table 4).

Our study has limitations. We explored only two patterns of mixing between consecutive recipients of injections with unsafe equipment, random and age-dependent (assortative), reasoning that the true mixing pattern will lie somewhere between the two. The posterior proportion of all-age HIV incidence caused by injections was constrained by the very low HIV incidence observed among 5- to 12-year-olds. A mixing pattern that resulted in reduced exposure of 5- to 12-year-olds to contaminated unsafe injections compared with the age-dependent pattern might, therefore, be consistent with a higher transmission probability from unsafe injections, leading to higher posterior estimates of the all-age proportion of HIV incidence attributed to unsafe injections. However, because this age group has the lowest HIV prevalence, it is difficult to postulate a lower-risk group with which 5- to 12-year-olds could share injection equipment. It is therefore reasonable to think of the age-dependent estimates as an upper bound to the true values.

The results of previous attempts to assess the importance of unsafe injections in HIV transmission in sub-Saharan Africa by fitting regression models to data from observational studies have been equivocal. Some studies have found no strong evidence of an association between injections and HIV incidence, although risk ratios for HIV incidence associated with injections as high as ≈1.5 for the association between HIV incidence and injections could not be excluded (12, 13), whereas others have found prior injections to be associated with the risk of HIV infection (14–17). Such studies are undoubtedly valuable, but the likely importance of residual confounding and reverse causality represent serious threats to the validity of their conclusions. Moreover, such studies do not allow the proportion of transmission attributable to different routes to be directly estimated.

Our results are broadly consistent with the qualitative findings of a study that used an age-structured deterministic compartmental model to determine whether transmission through heterosexual contact or unsafe injections could predict the observed adult HIV prevalences in various sub-Saharan African countries (10). In this study, the two routes of transmission were modeled separately and the authors concluded that, unlike heterosexual transmission, unsafe injections were unable to explain all of the observed HIV prevalences. Unlike our study, this approach did not allow the authors to estimate how much HIV transmission was likely to be due to each route of transmission.

Our findings are likely to generalize to other populations in sub-Saharan Africa because they were primarily determined by the low rates of HIV infection among 5- to 12-year-olds relative to other age groups, an observation common to many other populations in sub-Saharan Africa (14, 18–21). Indeed, any claim that transmission from unsafe injections represents a large proportion of overall HIV incidence must provide a plausible explanation for how this age group escapes infection.

Materials and Methods

Data. HIV incidence and prevalence, injection, and fertility rates were calculated from a general population cohort in rural Masaka (1989–2000) (11, 22, 23). Transfusion rates and transfusion and injection safety were estimated from observational studies in Masaka and Mbarara districts, Uganda, and the WHO region that includes Uganda (9, 13, 24–29). HIV transmission probabilities were estimated from a systematic literature review and other observational studies (1, 4, 6–8, 30).

Infection Model. The expected annual HIV incidence risk due to unsafe injections in age group j, I_j, was calculated as

$$I_j = 1 - (1 - p_c\, p)^{r_j q}, \qquad [1]$$

where p_c is the probability that an unsafe injection is contaminated, p is the probability of transmission from a contaminated unsafe injection, r_j is the number of injections per HIV uninfected person per year in age group j, and q is the probability that an injection is unsafe (reused in the absence of effective sterilization).

In the main analysis q was taken as the product of the probability of reusing injection equipment without the use of a sterilizer and the probability that partial washing and heating of injection equipment had not inactivated HIV. The prior for the former was derived from a two-stage cluster sample survey of the general population in Mbarara district, Uganda, in 2001 (9), and the latter was taken to be uniform on (0, 1) i.e., any value between 0 and 1 was equally likely. Two further sensitivity analyses assumed priors for q that were (*i*) uniform on (0, 1), or (*ii*) derived from a random effects model using data on injection safety throughout the WHO region "E" that included Uganda.

Under the random mixing assumption p_c was given by

$$p_c = \frac{\sum_j r'_j n'_j}{\sum_j (r_j n_j + r'_j n'_j)}, \quad [2]$$

where r_j and r'_j are the annual injection rate in age group j among HIV uninfected and infected people, and n_j and n'_j are the numbers of HIV uninfected and infected people. Under the age-dependent mixing assumption, p_c varied by age group and was calculated as above but by using only values of r_j, r'_j, n_j, and n'_j from the same age group.

The expected annual HIV incidence risk due to unsafe blood transfusions was calculated similarly, except that the rates and probabilities refer to blood transfusions and the probability that an unsafe blood transfusion was contaminated was estimated by using HIV prevalence among blood donors in Masaka as shown in *SI Text*.

The expected annual HIV incidence risk among HIV uninfected 0- to 4-year-olds due to mother-to-child transmission (I_M) was estimated by calculating the number of children born per year infected with HIV via mother-to-child transmission, divided by the number of HIV uninfected 0- to 4-year-olds:

$$I_M = \frac{p_M \sum_k S_k f_k}{N}, \quad [3]$$

where p_M is the probability of mother-to-child transmission of HIV per infant born to an infected mother, S_k is the number of HIV infected women in age group k, f_k is the fertility rate of HIV infected women in age group k, and N is the mean number of HIV uninfected 0- to 4-year-olds. We assumed all mother-to-child transmission occurred among 0- to 4-year-olds, including transmission that occurred before birth.

Annual incidence risks were calculated for 0- to 4-, 5- to 12-, and ≥13-year-olds and overall by transmission route, and converted to rates for comparison with data.

Statistical Analysis. Confidence intervals for HIV incidence and injection rates were based on the Poisson assumption; for HIV prevalence they were based on the normal approximation to the binomial distribution. Uncertainty in all parameter values was accounted for through the specified prior distributions: Beta distributions for proportions and probabilities, and gamma distributions for rates. When data allowed informative priors to be specified, they were calculated where possible (injection rates, HIV prevalence, fertility rates, probability of unsafe injections) by using the fact that these distributions are conjugate priors for binomial and Poisson distributions respectively. When it was not possible (transmission probabilities from mother-to-child, for transfusions and injections, and probabilities transfusions were unsafe and contaminated), priors for parameters were chosen to have the same expected values as estimates of these parameters and so that ≈95% of the probability fell within the 95% confidence intervals. Extending the approach of Gisselquist (1), the prior for the probability of transmission from a deep percutaneous wound, d, was derived by using the relationship $d = bc/(a(1 - b) + bc)$, where b is the risk of transmission from all percutaneous wounds, c is the probability that the wound is deep given that transmission from a percutaneous wound occurred, and a is the probability that the wound is deep given that no transmission from a percutaneous wound occurred. Priors for a and c were derived from a case control study (7), whereas the prior for b was derived from a cohort study (8). Full details of prior specification are published as *SI Text*.

The priors and infection model provide initial predictions of HIV incidence attributable to each transmission route in the three age groups. The posteriors show how these predictions should be modified in light of the HIV incidence data. If D denotes the data; θ, the model parameters; $p(\theta)$, the prior distribution of the parameters; and $p(D|\theta)$, the likelihood of the data given the model and parameters, then Bayes' theorem implies that $p(\theta|D) \propto p(D|\theta)\,p(\theta)$, where $p(\theta|D)$ is the posterior distribution. The likelihoods of the observed numbers of incident cases in 0- to 4- and 5- to12-year-olds, $p(D|\theta)$, were calculated assuming these were drawn from a Poisson distribution, with means equal to the expected incidence in each age group due to the three modeled transmission routes (injections, transfusions, and mother-to-child transmission). Posterior inference was performed by using a Markov chain Monte Carlo algorithm using WinBUGS version 1.4.1 (31). This software was also used to evaluate the prior model by simulation. Results were based on 1,010,000 samples from the Markov chain so that every 10th iteration was recorded and the first 10,000 samples were taken as burn-in and discarded. Convergence was assessed by visual inspection of trace plots (SI Fig. 5) and, more formally, using the Gelman–Rubin convergence statistic. Model code is shown in *SI Text*.

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