The estimated risk of SARS-CoV- 2 infection via cornea transplant in Canada

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Abstract In late 2019 the respiratory illness, Corona Virus Disease-19 caused by the SARS-CoV-2 virus emerged in China and quickly spread to other countries. The primary mode of transmission is person-to-person via respiratory droplets. SARS-CoV-2 has been identified in conjunctiva. Transmission by cornea transplant has not been reported but is theoretically possible. We aimed to estimate the possible risk of transmission in Canada via cornea transplant during the first wave of the pandemic, and the potential risk reduction from testing decedents. We constructed a deterministic model in which the risk of transmission was estimated as the product of three proportions: decedents with SARS-CoV-2 infection, corneas that are NAT positive, and NAT positive corneas presumed to transmit. Risk was estimated according to 3 scenarios: most likely, optimistic and pessimistic. At the peak of the first wave of the pandemic risk was

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estimated to be 1 in 63,031 cornea transplants in Canada but could be as low as 1 in 175,821 or as high as 1 in 10,129. It would take 16 years at the peak infection of the first wave of the pandemic to observe 1 transmission. Testing would reduce the risk of 1 in 63,031 to 1 in 210,104 assuming 70% test sensitivity. The theoretical risk of SARS-CoV-2 transmission by cornea transplant is extremely low and decedent testing is unlikely to be beneficial.

Introduction

Cornea transplantation is one of the most common transplantation procedures, improving vision, reducing pain and increasing quality of life. In Canada, nearly 5000 cornea transplantations are performed each year, of which over 4000 are domestically sourced (Canadian Eye and Tissue Data Committee 2016). Viable corneas for transplantation are maintained in hypothermic preservation solution for up to 14 days, hence regular harvesting from deceased donors is essential to meet transplantation demand.

In late 2019, a novel virus, SARS-CoV-2, which primarily causes respiratory symptoms (SARS-CoV-2, COVID-19), was identified in Wuhan, China (World Health Organization 2020), and quickly spread to other countries. By March 2020, cases were being identified in Canada. In March, an urgent teleconference meeting of the Canadian Eye and Tissue Donation Community was held, bringing together eye and tissue donation and bank leaders from across the country. Participants included administrative, medical and quality directors from banks, donation organizations, regulatory and professional associations. It was (and still is) unclear whether SARS-CoV-2 can be transmitted by tissues from an infected donor to a recipient; however, at this time there is insufficient evidence to refute this possibility (Ho et al 2020). One of the urgent issues identified by the team was to estimate the risk of SARS-CoV-2 transmission via tissue transplantation, assuming that transmission is possible. Compared to most banked tissues, corneas require less processing between the harvesting and storage steps and might thus be more susceptible to

disease transmission than other transplants. Moreover, reports suggest that the eye is a possible route of entry for SARS-CoV-2 (Ho et al 2020), and that some cells from ocular tissues might be permissive for viral replication. Given that more extensive processing is likely to reduce tissue contamination by SARS-CoV-2, the cornea was chosen as worst-case scenario for estimating the risk of SARS-CoV-2 transmission by tissue transplantation.

In Canada, eye and tissue banks have added screening questions to identify and exclude donors potentially infected or exposed to SARS-CoV-2. Testing tissue donors for SARS-CoV-2 by nasopharyngeal and oropharyngeal nucleic acid amplification testing (NAAT) or serological testing (when available) is performed at the discretion of the medical director. The American Association of Tissue Banks (2020) has reported that the Food and Drug Administration (FDA 2020) does not recommend testing of asymptomatic donors. Recommendations from the Eye Bank Association of America (EBAA) and the Global Alliance of Eye Bank Associations (GAEBA) are in line with those of the FDA (Desautels et al. 2020). Given that regulatory bodies currently do not require testing of tissue donors for SARS-CoV-2 infection, yet a theoretical risk of transmission by tissue transplantation still exists., We have developed and tested a mathematical model aimed at quantifying this risk.

Methods

The risk of a corneal transplant transmitting SARS-CoV-2 without testing was estimated from the product of three terms:

$$\text{Risk}_{CT} = P_{\text{Unidentified}} \times P_{\text{NATpos}} \times P_{\text{Transmit}}$$

The proportion of the general population with asymptomatic or mild infection that clinicians would not be aware of ($P_{\text{Unidentified}}$) was estimated from the number of unresolved cases and adjusted for the proportion who would be in the pre-symptomatic period, thus not included in the reported cases (see Table 1). The proportion of patients that would have SARS-CoV-2 NAT-positive conjunctival tissue ($P_{\text{NAT pos}}$) was estimated from a meta-analysis of studies in which patients with known SARS-CoV-2 infection and with conjunctivitis had eye exudate or tears tested for SARS-CoV-2 nucleic acid (See

Table 1 Parameters for most likely scenario

Parameter	Approach	Parameter value	Data sources
Prevalence of active COVID-19 infection	([N unresolved infections[A]/pop[B]] $\times$ 4[C]) + [N unresolved infections/pop] $\times$ 2.3/14 days (presymptomatic period)[D]	Varies by date and region	A: Public Health Agency of Canada (2020b)
			B: Statistics Canada (2020)
			C: Tuite et al (2020)
			D: He et al (2020b)
Probability of virus present in the tissue if donor is infected	Incidence of conjunctival congestion in COVID-19 positive patients	1.95% (CI 0.74–4.1)	Sarma et al (2020)
Probability of transmission		50%	Assumption
Sensitivity of nasopharyngeal swab testing	NAT vs CT, 1-sensitivity	30%	Fang et al (2020)

Table 1). In the absence of high-quality data, the proportion of corneas from decedents with NAT-positive eye exudate or tears that would transmit (P_{Transmit}) was theoretical and assumed to be 50%.

Given the uncertainty in the values of some parameters, the risk was estimated according to three scenarios: (1) a "most likely" scenario, which we considered to reflect the actual risk, given the current state of knowledge, albeit with an appropriate level of caution (2) an "optimistic" scenario, in which parameter values were adjusted so as to attenuate the risk; and (3) a "pessimistic" scenario, in which parameters values were adjusted according to a "worst-case" scenario (see Table 2 for details). The proportion of infected corneas that would transmit SARS-CoV-2 if transplanted was also varied from the assumed 50% to 25% and 10%, to compare the impact of this parameter

adjustment. In order to estimate the risk associated with hypothetical decedent testing, the estimated risk was multiplied by (1—(sensitivity of current assays)), with sensitivity estimated at 70% (Fang et al. 2020). However, given the uncertainty regarding assay sensitivity on cadaveric decedent samples, especially as mucosal specimen sampling might be impacted by post-mortem drying, parameter values of 50% and 80% were also tested.

This analysis makes a number of assumptions, the most important being:

1. It is assumed that SARS-CoV-2 can be transmitted via infected corneas.
2. Deceased donors with known SARS-CoV-2 infection would not be selected for cornea harvesting, thus risk estimates are solely based on

Table 2 Parameters for optimistic and pessimistic scenarios

Optimistic scenario	
Prevalence of active infections	Assumed to be 3 times the reported cases, rather than 4 for most likely scenario
Probability of virus in tissue if infected	0.74% (lower end of confidence interval)
Probability of transmission	50%

Pessimistic scenario	
Prevalence of active infection	Assumed to be 3 times the reported cases, with a pre-symptomatic period of 3 days
Probability of virus in tissue if infected	4.1% (upper end of confidence interval)
Probability of transmission	50%

infectionsed donors that neither physicians nor families are aware of.

3. The proportion of SARS-CoV-2 positive decedents is equal to the proportion of people with SARS-CoV-2 that have not been identified by testing and is 4 times the proportion of individuals with known infections.

4. The probability of NAT-positive corneas can be estimated from studies of NAT testing in patients with eye symptoms, and those without eye symptoms are assumed to have NAT-negative corneas and thus cannot transmit the infection.

5. 50% of decedents with NAT-positive corneas will transmit infection to recipients.

We note that our model assumes independence of the three terms. However, it is possible that they are not independent. For example, for decedents whose only symptom is conjunctivitis there may be less suspicion of infection, thus greater risk of transmission. Alternatively, a decedent with no symptoms may be less likely to have conjunctival viral particles, thus less risk of transmission. To address this possibility a sensitivity analysis was performed in which risk was estimated assuming potential negative correlations of 10%, 15% and 20% and potential positive correlations of 10%, 15% and 20% in the most likely scenario.

Results

The risk of SARS-CoV-2 infections varies according to the prevalence of active infections in the community and was very low in the early stage of the first phase of the pandemic from mid-March to mid-April 2020, and highest from mid-April to mid-July (Fig. 1). According to the most likely scenario, the risk at the peak of the first phase of the pandemic was about 1 transmission in 63,000 cornea transplants, but might have been as low as 1 in 175,000, or as high as 1 in 10,000, depending on whether an optimistic or a pessimistic scenario is tested (Table 3). These estimates assume that 50% of NAT-positive corneas would transmit the infection if transplanted. If the transmission rate was 25%, the risk would be proportionally lower, at about 1 in 126,000 transplants, and for a transmission rate of only 10%, the risk would be about 1 in 315,000, according to the most likely scenario. As the peak active infection rate varied across provinces, so did the peak risk, with the highest risk in Quebec at about 1 in 1600 transplants, and the lowest in British Columbia at 1 in 415,000 transplants, according to the most likely scenario. The same scenario yields an average risk over that period of 1 in 63,061 across Canada. If about approximately 4000 cornea transplants are performed each year in Canada, it would take ∼ about 16 years for one infection to be transmitted by cornea transplantation. In sensitivity analyses that considered potential positive and negative correlation among the terms in the equation, varying the coefficient correlation from -20% to + 20% had a modest impact on risk estimates (See Appendix Table 1).

If decedent testing was performed, assuming that 70% of infected donors would be identified, the risk would be proportionally reduced (Table 4). For
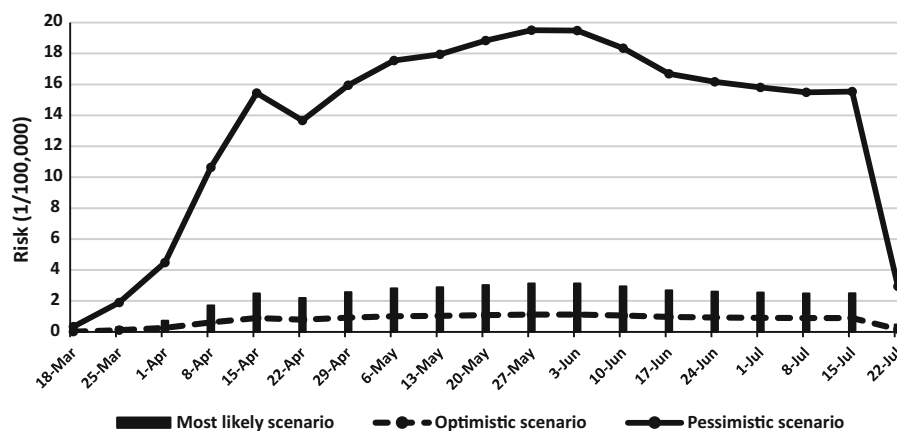
Fig. 1 Risk of cornea transplant transmission in Canada according to three scenarios, from March 18 to July 22, 2020

Table 3 Risk of SARS-CoV-2 transmission by cornea transplantation by province at their respective peak week in number of COVID-19 cases between March and June 2020

Province	Transmission risk		
	Most likely scenario	Optimistic scenario	Pessimistic scenario
British Columbia	1 in 414,988	1 in 1,157,578	1 in 66,685
Alberta	1 in 82,216	1 in 229,334	1 in 13,211
Saskatchewan	1 in 227,043	1 in 633,319	1 in 36,484
Manitoba	1 in 327,331	1 in 913,064	1 in 52,599
Ontario	1 in 94,671	1 in 264,078	1 in 15,213
Quebec	1 in 16,490	1 in 45,998	1 in 2,650
Newfoundland and Labrador	1 in 119,971	1 in 334,651	1 in 19,279
New Brunswick	1 in 388,115	1 in 1,082,618	1 in 62,367
Nova Scotia	1 in 94,527	1 in 263,677	1 in 15,190
Prince Edward Island	1 in 354,139	1 in 987,844	1 in 56,908
Canada	1 in 63,031	1 in 175,821	1 in 10,129

example, across Canada the peak risk would be reduced from about 1 in 63,000 transplants to about 1 in 210,000 transplants.

Discussion

Current evidence indicates that SARS-CoV-2 transmission via cornea transplant from an infected donor is merely a theoretical risk; yet, not a single case of transmission through this mode has been reported as of January 4, 2021 (FDA). However, it might take a while before undisputable cases of transmission are identified, for several reasons. First, it might be difficult to distinguish transplant-acquired and community-acquired infections. Second, transmission might not be ascertained, especially if the recipient remains asymptomatic. Finally, as suggested by our analysis, transmission by cornea transplant is likely a very rare event. Until such time as transmissibility is confirmed or refuted, it is prudent to assume that it may be transmissible.

Upon harvest, corneas are stored in Optisol-GS solution, which contains dextran and chondroitin sulphate to control stromal hydration, as well as vitamins and ATP precursors, but no antiviral agents. Storage is maintained at 2–8 °C. Recent evidence suggests that SARS-CoV-2 infectivity is better maintained by cold temperatures (4 °C) than by storage at room temperature (Chin et al. 2020; Chan et al. 2020). Corneas may be stored for up to two weeks, but transplantation within one week from harvest is preferred. Thus, if SARS-CoV-2 survives the storage process, as suggested by some stability studies, a theoretical risk remains.

Our model accounted for the likelihood of a cornea transmitting SARS-CoV-2 from a deceased donor who was positive for the infection. We assumed that donors with known infections would be excluded from cornea harvesting due to because of screening criteria in place, although it is possible that symptomatic donors would not be identified by the physician, or that symptoms would not reported by the deceased donor's relatives. The proportion of deceased donors with known infections was based on public health data, if only one out of five infections would be identified, which would lead to unintended harvesting of corneas from infected donors. The proportion of infections identified by public health is dependsent on testing policies, which vary by jurisdiction and over time. Thus, it is possible that more people had symptoms than were tested (but would be identified by relatives in the case of a deceased tissue donor) and that the proportion of infected decedents with no known symptoms might be less lower than expected. Hence, it is possible that our estimate of the proportion of decedents with SARS-CoV-2 infection was not underestimated, and might have been rather conservative.

We have also assumed that the proportion of decedents who might have donated infected corneas could be estimated from reports of the proportion of infected patients with eye or conjunctival symptoms, and reports of the proportion of these patients that were positive for SARS-CoV-2 nucleic acid in the eye. Although we believe that this is the best strategy for quantifying these parameters at this time, there is inherent uncertainty in these estimations, for at least two reasons: (1) there are relatively few published data

Table 4 Risk of SARS-CoV-2 transmission by cornea transplantation in Canada at the peak week in number of cases between March and June 2020 according to three scenarios, and expected impact of donor testing with test sensitivities of 50%, 70%, and 90%

Testing strategy and sensitivity	Transmission risk								
	Assuming 50% of NAT-positive donors transmit infection			Assuming 25% of NAT-positive donors transmit infection			Assuming 10% of NAT-positive donors transmit infection		
	Most likely scenario	Optimistic scenario	Pessimistic scenario	Most likely scenario	Optimistic scenario	Pessimistic scenario	Most likely scenario	Optimistic scenario	Pessimistic scenario
Without testing	1 in 63,031	1 in 175,821	1 in 10,129	1 in 126,062	1 in 351,641	1 in 20,257	1 in 315,156	1 in 879,103	1 in 50,643
With testing									
50% sensitivity	1 in 126,062	1 in 351,641	1 in 20,257	1 in 252,125	1 in 703,282	1 in 40,515	1 in 630,311	1 in 1,758,205	1 in 101,286
70% sensitivity	1 in 210,104	1 in 586,068	1 in 33,762	1 in 420,208	1 in 1,172,137	1 in 67,524	1 in 1,050,519	1 in 2,930,342	1 in 168,810
80% sensitivity	1 in 315,156	1 in 879,103	1 in 50,643	1 in 630,311	1 in 1,758,205	1 in 101,286	1 in 1,575,778	1 in 4,395,513	1 in 253,216

on SARS-CoV-2 infection in the eye; and (2) it is possible that corneas might be infected in the absence of conjunctivitis or exudate.

Our model also assumed that not all SARS-CoV-2—contaminated corneas would transmit the infection. If indeed SARS-CoV-2—contaminated corneas could transmit the infection through transplantation, it is unlikely that transmission would occur for 100% of contaminated corneas. Given the paucity of available high-quality data, we assumed that 50% of transplanted SARS-CoV-2-positive corneas would establish an infection. As mentioned earlier, this figure may nonetheless represent an overestimate. In a recent study, SARS-CoV-2 RNA was detected in the corneal discs of 6 out of 11 (55%) deceased patients with COVID-19 (Casagrande et al 2021). Of note, most patients included in this study had severe COVID-19 illness (i.e., 10 [91%] died of COVID-19) and hence exhibited high viral loads. Despite that, none of these corneal discs demonstrated infectivity when incubated with a cell line. Establishing an infection depends on a range of factors including the infectious dose, the route of entry, and several host factors such as immune status, age, overall health, etc. Importantly, the cornea is not a vascular tissue; thus, it might be resistant to infection, and might act merely as a carrier of infectious virions. Therefore, the true risk of SARS-CoV-2 transmission through cornea transplantation is probably even lower than the estimates presented in the current study.

Several observations point to the importance of maintaining a high level of vigilance regarding the risk of transmission of COVID-19 by cornea transplantation. First, numerous reports have documented the detection of SARS-CoV-2 RNA in ocular tissues (Xia et al. 2020; Li et al 2020; Zhou et al 2020; Wu et al 2020; Chen et al 2020a,b,c; Zhang et al 2020a,b,c; Sarma et al 2020; Colavita et al 2020). Second, one research team was able to demonstrate infectivity in ocular samples from COVID-19 patients by inoculation of cell lines that are permissive for SARS-CoV-2 infection (Colavita et al 2020); however, Seah et al (2020) and Li a et al. (2020) did not succeed in demonstrating infectivity of ocular samples in cell culture. Third, the ACE2 viral receptor and the TMPRSS2 serine protease required for cell entry are expressed in a variety of tissues and organs (Hamming et al 2004; Zou et al 2020; Muus et al. 2021; Sungnak et al 2020; Ziegler et al 2020; Li b et al. 2020; Fu et al

2020; Chen b et al. 2020; Hikmet et al 2020; Battagello et al 2020; Dong et al 2020; Singh et al 2020; Ortiz et al 2020) including ocular tissues (Sungnak et al 2020; Ma et al. 2020, Makovoz et al 2020, Hamashima et al 2020, Collin et al. 2021). Fourth, there is experimental evidence that SARS-CoV-2 can infect cells from human ocular tissues ex vivo (Makovoz et al 2020; Hui et al 2020). Additionally, Deng et al (2020) were able to infect a non-human primate via the conjunctival route. Collectively, these reports suggest that the eye is a possible route of entry for SARS-CoV-2, and that some cells from ocular tissues might be permissive for viral replication.

The contribution of the scientific literature in the evaluation of the risk of SARS-CoV-2 transmission by cornea transplantation should be assessed in a broader context. COVID-19 remains essentially a respiratory tract infection. Reports of COVID-19 – associated conjunctivitis are anecdotal, and generally involve more severe cases of COVID-19. To the best of our knowledge, there have is been very fewone reported cases suggesting that for which the eye wasmay have been the primary route of infection (Lu et al. 2020)., and Even in these very few cases, one cannot exclude the possibility that the virus entered the body via the respiratory system. Some authors have mentioned the anatomical connection between the nasolacrimal system and the upper respiratory airways as a possible route by which the virus could be carried from one compartment to the other (Belser et al 2013). The results of an experimental infection in a non-human primate animal model are consistent with this hypothesis (Deng et al 2020). Nonetheless, the available evidence strongly suggests that aside from anecdotal reports, virtually all COVID-19 cases result from primary infection of respiratory airways.

In the context of our risk assessment related to cornea transplantation, another remote possibility is that the virus could spread from a contaminated cornea transplant to other organs, including the lungs, via the lymphatic and circulatory systems, in a sort of retrograde movement from the basolateral side to the apical side of alveolar epithelial cells, which are prime targets for viral infection and tissue damage (Mason 2020). We believe that this hypothesis is unlikely, as it would imply that viral particles are able to cross endothelial cells, basement membranes, and interstitial spaces in the lung before finally reaching alveolar epithelial cells. Although the ACE2 receptor is

expressed by diverse cells from several organs, the level of expression of ACE2 in a given cell type is not a reliable predictor of the susceptibility of that cell to SARS-CoV-2 infection (Oritz et al. 2020; Bojkova et al. 2021). Even in the worst-case scenario of a cornea transplant from an asymptomatic SARS-CoV-2—positive donor, the available evidence and the results presented herein suggest that the risk of a transplant recipient developing a respiratory infection typical of COVID-19 appears to be very low.

Decedent testing prior to harvesting is not routinely performed in Canada, but it has been under consideration by various eye banks as a potential risk reduction strategy. A multifactorial approach considering clinical presentation, epidemiology/risk factors, laboratory tests and imaging has been suggested for the early identification of COVID-19 cases (Ai et al 2020; Qin et al 2020; Chen et al 2020c). Such a multifaceted strategy might reduce the chances of false-negative diagnoses. The sensitivity of NAT has been shown to fluctuate between studies, and may be impacted by several variables including: comparator or gold standard chosen (Zhang et al. 2020b,c), timing of sampling (Chen et al. 2020b), sample quality, anatomical site of sampling in the respiratory tract (LeBlanc et al. 2020; Vlek et al. 2021), assay used (van Kesteren et al. 2020) and clinical presentation. Compared to a COVID-19 reference standard, reported sensitivities range from 71 to 83% (Fang et al 2020; Long et al 2020; He et al 2020a), and a recent meta-analysis of seven studies suggests that the sensitivity of NAT on nasopharyngeal swab/aspirates and throat swab specimens was 73.3% (95% CI 68.1–78.0%) (Böger et al 2020). Nasopharyngeal samples obtained from decedents might have lower sensitivity due to drying of tissues prior to sampling. We have estimated the risk reduction provided by NAT performed on decedent samples using a sensitivity of 70%, but we have also assessed the impact of sensitivities as low as 50% and as high as 80%.

Our results suggest that the risk of SARS-CoV-2 transmission via cornea transplant is low in Canada, even when using relatively high prevalence data from the peak of the first wave of the pandemic. Risk varies as a function of the prevalence in the population but is systematically much lower than the risk of being infected by the conventional route of the respiratory tract. For example, assuming there are four undiagnosed cases for every diagnosed case in the general population, with a peak incidence of 2000 daily cases

(Public Health Agency of Canada 2020a), about 1 in 5,000 people would be expected to be infected at the peak infection rate, whereas the risk from a cornea transplant would be much lower, at about 1 in 63,000 as per our estimates. According to the pessimistic scenario, the risk would be about 1 in 10,000, if there are ten undiagnosed cases for every positive diagnosis. With that assumption, the proportion of the general population that would be infected is about 1 in 2000.

Decedent testing would reduce the risk as a function of the sensitivity of the assay. For example, a risk of 1 in 63,000 at the peak of the pandemic could have been reduced to about 1 in 210,000 if testing had a sensitivity of 70%. During non-pandemic times, about 100 cornea transplants are performed each week in Canada, and since most elective surgeries were cancelled during the peak of the pandemic, the number of transplants performed during that period must have been lower. Given that the SARS-CoV-2 transmission risk associated with cornea transplantation, based on our estimates, is already very low, the benefit of decedent testing appears to be negligible.

Declarations

Conflict of interest Steven J. Drews has acted as a content expert on respiratory viruses for Johnson and Johnson (Janssen). He also has acted as a content expert to Roche on Arboviruses. All other authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval Not applicable.

Consent for publication All authors consent to publication of this manuscript.

Appendix

See Table 5

Table 5 Sensitivity analysis of potential non-independence: Risk of SARS-CoV-2 transmission by cornea transplantation in Canada at the peak week in number of cases between March and June 2020 and expected impact of donor testing with test sensitivities of 50%, 70%, and 90%

Testing strategy and sensitivity	Assuming 50% of NAT-positive donors transmit infection Transmission risk						
	Most likely scenario	Potential negative correlation[a]			Potential positive correlation[a]		
		− 10%	− 15%	− 20%	+ 10%	+ 15%	+ 20%
Most likely scenario							
Without Testing	1 in 63,031	1 in 70,035	1 in 74,154	1 in 78,789	1 in 57,301	1 in 54,810	1 in 52,526
With testing							
50% sensitivity	1 in 126,062	1 in 140,069	1 in 148,309	1 in 157,578	1 in 114,602	1 in 109,619	1 in 105,052
70% sensitivity	1 in 210,104	1 in 233,449	1 in 247,181	1 in 262,630	1 in 191,003	1 in 182,699	1 in 175,086
80% sensitivity	1 in 315,156	1 in 350,173	1 in 370,771	1 in 393,945	1 in 286,505	1 in 274,048	1 in 262,630

[a]Correlation between three risk component terms: $P_{\text{Unidentified}}$, $P_{\text{NAT pos}}$ and P_{Transmit}

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