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Estimating the risk reduction of isolation on COVID-19 nonhousehold transmission and severe/critical illness in nonimmune individuals: September to November 2021

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Abstract

There is growing scientific interest in immunity mandates/passports (IMP) for viral diseases in light of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. IMP isolate those who remain nonimmune from various settings to reduce nonhousehold transmissions from the nonimmune and reduce severe/critical illness among the nonimmune. A major limitation in the scientific literature is that there are currently no methods to quantify how many nonimmune individuals need to be isolated to achieve these purported benefits. This paper develops a procedure for estimating the benefits of IMP using a novel variant of the number needed to treat which we call the number needed to isolate (NNI). We use data from the SARS-CoV-2 pandemic to demonstrate the properties and utility of the NNI and to inform the debate about IMP. We focus on data from the European Union, United Kingdom, United States, Canada, Australia, and Israel during the fall 2021 when the Delta (B.1.617.2) variant predominated.

KEYWORDS
COVID-19, critical illness, SARS-CoV-2, severe illness, transmission

1 | INTRODUCTION

There is growing scientific interest in immunity mandates/passports (IMP) for viral diseases in light of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. IMP isolate those who remain nonimmune from various settings (e.g., work, leisure, transportation, etc) to (i) reduce nonhousehold transmissions from the nonimmune and (ii) reduce severe/critical illness among the nonimmune. IMP isolate nonimmune individuals from various settings, thus limiting their (i) contact with others and (ii) exposures and, in turn, their risk of developing a severe/critical infection. This is in addition to the goal of incentivizing vaccination. In many ways, isolating nonimmune individuals is an extension of the principle that we should isolate infectious or potentially infectious cases (contact isolation) or cases at high-risk of morbidity/mortality (pre-emptive isolation) to reduce the risk of transmission and severe/critical illness. Whether we are isolating these cases in medical wards, long-term care facilities, or countries, the rationale is the same. The difference is merely of scale. A major limitation in the scientific literature is that there are currently no methods to quantify how many nonimmune individuals need to be isolated to achieve these purported benefits on non-household transmission and severe/critical illness.

Quantification of the benefits is essential if we want to perform a cost–benefit analysis of IMP.

The number needed to treat (NNT) is helpful in this regard. The NNT is 1 divided by the absolute risk reduction (ARR) on an intervention (NNT = 1/ARR).[1] The NNT is the number of people who need to receive a treatment (e.g., statins) to prevent one outcome (e.g., myocardial infarction) over a period of time. This commonly used metric can be extended quite easily to IMP. To understand how, consider the following. To justify isolation at any scale, a group of individuals should be *at risk* of the outcome we're concerned about, not merely in relative terms ('Group A vs. Group B') but more importantly in absolute terms ('Group A's risk is 1 in X'). This is because relative risks (RRs) don't tell us if a risk is clinically meaningful, whereas absolute risks (ARs) do. Therefore, the justification for IMP rests on the hypothesis that nonimmune individuals are at high AR of nonhousehold transmission and severe/critical illness, thereby warranting isolation. In essence, these ARs *are* the ARRs of IMP on these outcomes because isolating nonimmune individuals removes these risks from the general population. In other words, by removing nonimmune individuals from a setting, we remove their AR from that setting, such that the ARR of IMP is simply this AR. Like the NNT, one can quantify the risk reductions gained from IMP by taking the reciprocal of these ARs, which converts these probabilities into a more intuitive form ('1 in X'). This becomes what can be called the 'number needed to isolate' (NNI), which is the number of nonimmune individuals needed to isolate to prevent (i) one transmission event in a given type of nonhousehold setting or (ii) one case of severe/critical illness.

This paper seeks to outline a method for estimating the NNI using data from the SARS-CoV-2 pandemic as a case example. We chose this case example to demonstrate this procedure because IMP for SARS-CoV-2 started to be discussed/implemented in many countries during the fall 2021, notably the European Union (EU), United Kingdom (UK), United States (US), Canada, Australia, and Israel. The fall 2021 was a time when the Delta (B.1.617.2) variant predominated. The period from September 1 to November 26, 2021, was studied because the latter date was when Omicron (B.1.1.529) was declared a variant of concern. Shortly afterwards a new phase of the pandemic started where Omicron predominated. Therefore, the fall period before this date was the period of interest in this worked example of how one can estimate the NNI.

2 | METHODS

Estimating the NNIs for these outcomes requires estimating (i) the AR of a transmission event in nonhousehold settings (AR_{tr}) and (ii) the AR of severe (AR_{sv}) or critical (AR_{cr}) illness for the Delta variant in nonimmune individuals. AR_{tr} is the probability of a transmission event in a nonhousehold setting from a nonimmune person in the general population infected with the Delta variant. This risk is estimated by taking the combined probability of the risk of infection (IR) and the risk of transmission from a nonimmune person in that type of nonhousehold setting (e.g., healthcare). The latter is the secondary attack rate (SAR) of a Delta infection typically observed from nonimmune index cases in that type of setting:

$$NNI_{tr} = \frac{1}{ARR_{tr}} = \frac{1}{AR_{tr}} = \frac{1}{IR \times SAR}$$

ARR_{tr} is the ARR of isolation on transmission from nonimmune people in a given type of non-household setting. The combined probability is needed to estimate AR_{tr} because a person must be infected first before they can transmit SARS-CoV-2. Technically, this AR_{tr} is the risk of one transmission *event*, which may include one or more secondary infections. This is because the SAR is the proportion of infections among the contacts of an index case, such that the total number of secondary infections depends on the total number of contacts. For example, a SAR of 20% is consistent with 20/100, 2/10 and 1/5. AR_{tr} is the risk of one generation of transmission caused by the nonimmune index case, assuming they go into a setting of that type while infected. The IR is the point-prevalence of infectious cases in the general population, which is the estimated risk that a nonimmune individual is infected.

AR_{sv} and AR_{cr} are the probabilities that a nonimmune person in the general population gets a Delta infection which develops into a severe or critical illness, respectively. Given the steep age-risk gradient for severe/critical illness from SARS-CoV-2,[2] it is important to stratify these ARs by age. These ARs are estimated by taking the combined probability of the IR and age-stratified rates of severe illness (infection-severe rates, ISRs) and rates of critical illness (infection-critical rates, ICRs) among nonimmune individuals infected with the Delta variant. The combined probability is needed because one cannot develop a severe/critical illness unless one is first infected with SARS-CoV-2. Therefore, the NNI for severe illness is estimated:

$$NNI_{sv} = \frac{1}{ARR_{sv}} = \frac{1}{AR_{sv}} = \frac{1}{IR \times ISR}$$

and similarly for critical illness:

$$NNI_{cr} = \frac{1}{ARR_{cr}} = \frac{1}{AR_{cr}} = \frac{1}{IR \times ICR}$$

ARR_{sv} and ARR_{cr} are the ARRs of isolation on severe and critical illness, respectively, among nonimmune people in a given age-group.

Like the NNT, time is implicit in the NNI since it relates to the time window over which the risk was measured. These ARs are the risks on a given day (i.e., the day of the IR) because point-prevalence data are typically measured over 1 day. Moreover, the contact duration in most nonhousehold settings is typically less than 1 day. For these reasons, the NNI is the number of nonimmune individuals needed to isolate *on that day* (i.e., the day of the IR) to prevent one transmission event or one case of severe/critical illness. To show the risk reductions of isolation during a time period, NNIs can be calculated over time using daily IRs, which is what we did in this paper. This is an important difference between the NNI and NNT. For the NNI, the ARR is based on point-prevalence and the time window is 1 day. For the NNT, the ARR is typically based on incidence

proportion and the time window is often months or years. The rationale for using point-prevalence rather than other metrics (e.g., incidence, period prevalence, forecasted risks, etc) to estimate these ARs is detailed in the Discussion.

Daily IR point-estimates and 95% confidence intervals (CIs) from September 1 to November 26, 2021, inclusive were taken from the Defence Research and Development Canada (DRDC) database.[3] Its estimation methods are detailed online. The daily point-prevalence of infectious cases from this period were extracted for the EU member states, US states, Canadian provinces/territories, Australian states and the Capital/Northern Territory, and Israel. US county data were available and means were used to calculate state-level daily IRs. Data were extracted on January 25 to 28, 2022. The daily IR point-estimates in each region were used to calculate the NNIs on each day for nonhousehold transmission and severe/critical illness. Box and whisker plots were used to display the distribution of the NNIs during this period in each region to show the ARRs of isolating nonimmune individuals on these outcomes.

As noted, these IRs must be multiplied by estimates of the nonhousehold SARs, ISRs, and ICRs of nonimmune individuals infected with the Delta variant. Almost all the transmission data for the Delta variant involve households, which means the SARs of nonhousehold settings must be estimated. This can be done using known data on the nonhousehold SARs of the wild-type. There is a literature on these wild-type SARs since this was an area of focus during 2020. The COVID-19 vaccines were not available during this period. There was also relatively low natural immunity, as shown by the global median seroprevalence of SARS-CoV-2 antibodies in the general population in 2020 (median 4.5%, IQR: 2.4%–8.4%).[4] In other words, this data is ideal for our purposes because it captures the SARs of nonimmune index cases in different types of non-household settings. Therefore, the Delta SAR in a given type of nonhousehold setting (SAR_{Delta}) can be estimated by multiplying the wild-type SARs (SAR_{wt}) by a correction factor (CF_{Delta}= 1.97) to account for the increased transmissibility of Delta over the wild-type, which is about 97% more transmissible based on a global analysis of reproduction numbers[5]:

$$SAR_{Delta} = SAR_{wt} \times CF_{Delta}$$

A systematic search identified 7 meta-analyses of the wild-type SARs (see Supporting Information Appendix).[6–12] Delta SARs in six types of settings were estimated after applying this procedure to the mean SARs across these meta-analyses: households (mean SAR = 32.59%), social gatherings (mean SAR = 11.69%), casual close contacts (mean SAR = 3.05%), work/study places (mean SAR = 2.89%), healthcare (mean SAR = 2.96%), and travel/transportation (mean SAR = 4.40%) (Supporting Information: Table S1). The AR_{tr} for each non-household setting was estimated by multiplying its mean SAR by the IRs. Social gatherings are intimate settings where the intensity of contact is less than households but still high (e.g., gatherings of friends/family), whereas casual close contacts are lower intensity contacts (e.g., public areas/buildings). Notably, the estimated household SAR (32.59%) matched the observed mean SAR in a meta-analysis of household transmission of the Delta variant (29.7%, 95% CI: 23.0%–37.3%).[13] This suggests this procedure likely produced accurate estimates of the non-household SARs for Delta infections.

A similar procedure was needed for the ISRs and ICRs. A meta-analysis of seroprevalence studies to calculate age-stratified ISRs and ICRs for SARS-CoV-2 was available for this purpose.[14] The ISR was defined as those resulting in hospitalisation or out-of-hospital death. The ICR was defined as those resulting in ICU admissions or out-of-ICU deaths. The data were from early to mid-2020 when the wild-type predominated and immunity was low. Therefore, these ISRs and ICRs likely capture the risk of severe/critical illness in nonimmune people. For this reason, we extracted the mean ISR and ICR in each age-group in this report to estimate AR_{sv} and AR_{cr}. Age-stratified correction factors (CF_{Delta}) are needed to account for the increased severity of Delta versus the wild-type. For this we used the significant adjusted odds ratios for hospitalisation and ICU admission, respectively, of Delta versus wild-type infections from a large retrospective cohort (Supporting Information: Table S2).[15] The age-stratified ISR for the Delta variant was estimated:

$$ISR_{Delta} = ISR_{wt} \times CF_{Delta}$$

and similarly for critical illness:

$$ICR_{Delta} = ICR_{wt} \times CF_{Delta}$$

3 | RESULTS

From September to November 2021, IRs on any given day were typically ≤5% and stable in the UK and most of the EU (Figure 1 and Supporting Information: Figure S1). While there was regional variation, a similar temporal pattern of IRs was seen across the other regions we examined (Supporting Information: Figures S2-S8). Overall, the UK had the highest median daily IR from September to November 2021 (median 3.8%, IQR: 3.3%–4.0%), followed by the US Midwest (median 3.5%, IQR: 2.6%–4.5%), US West (median 3.4%, IQR: 2.1%–5.0%), US Northeast (median 2.3%, IQR: 1.5%–3.5%), US South (median 1.8%, IQR: 1.0%–3.2%), EU member states (median 1.3%, IQR: 0.4%–3.4%), Canada (median 0.5%, IQR: 0.1%–1.3%), Israel (median 0.08%, IQR: 0.02%–0.51%), and Australia (median 0.011%, IQR: 0.002%–0.069%) (Supporting Information: Figure S9).

Combining these IRs with other parameter estimates (Supporting Information: Tables S1-S2) from this worked example allowed us to estimate the NNIs for a nonhousehold transmission event and a case of severe/critical illness from September to November 2021. The NNIs for transmission in social gathering settings were lower in the United Kingdom and most EU countries compared to other nonhousehold settings (Figure 2). This may have been due to the combination of a higher SAR for social gatherings (11.69%) and

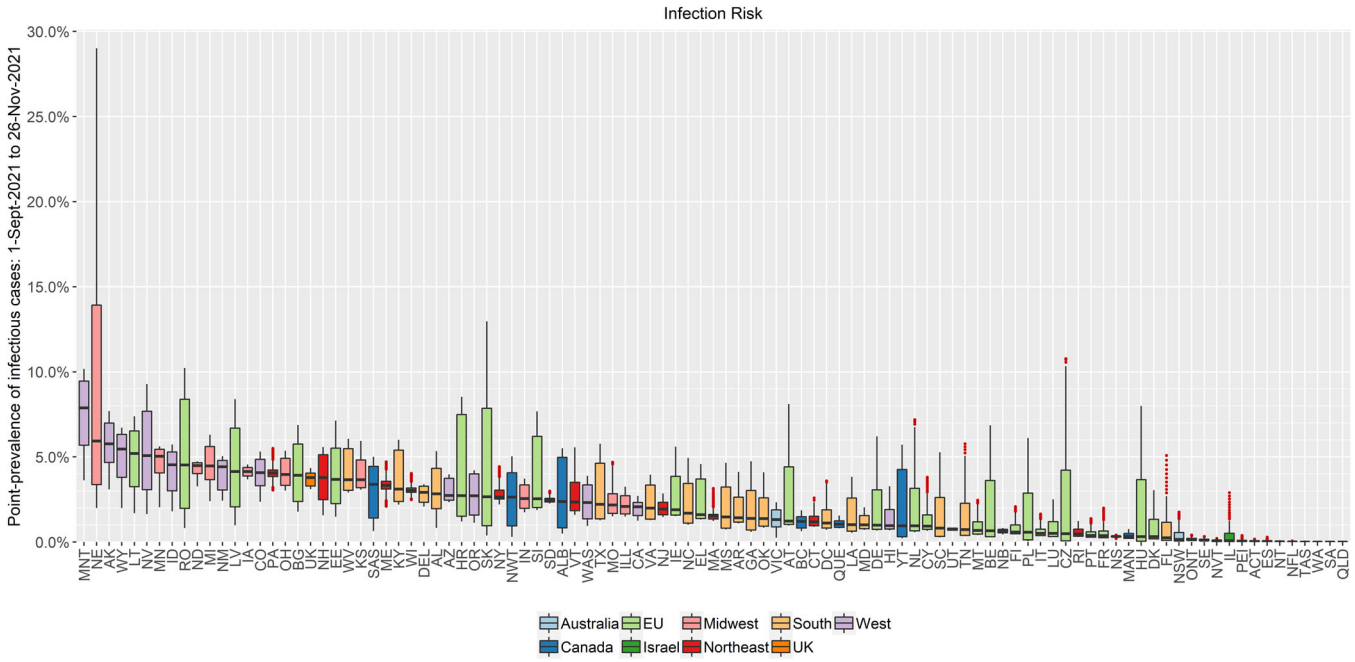

FIGURE 1 Daily infection risks from September 1 to November 26, 2021, by region and major jurisdiction. Major jurisdictions examined were EU member states, the UK, Israel, Canada, Australia, and the major US regions (Northeast, Midwest, South, West). The distribution of risks during this period are displayed using box-and-whisker plots. ACT, Australian Capital Territory; AK, Alaska; AL, Alabama; ALB, Alberta; AR, Arkansas; AT, Austria; AZ, Arizona; BC, British Columbia; BE, Belgium; BG, Bulgaria; CA, California; CO, Colorado; CT, Connecticut; CY, Cyprus; CZ, Czechia; DC, District of Columbia; DE, Germany; DEL, Delaware; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FL, Florida; FR, France; GA, Georgia; HI, Hawaii; HR, Croatia; HU, Hungary; IA, Iowa; ID, Idaho; IE, Ireland; IL, Israel; ILL, Illinois; IN, Indiana; IT, Italy; KS, Kansas; KY, Kentucky; LA, Louisiana; LV, Latvia; LT, Lithuania; LU, Luxembourg; MA, Massachusetts; MAN, Manitoba; MD, Maryland; ME, Maine; MI, Michigan; MO, Missouri; MN, Minnesota; MNT, Montana; MS, Mississippi; MT, Malta; NB, New Brunswick; NC, North Carolina; ND, North Dakota; NE, Nebraska; NFL, Newfoundland and Labrador; NH, New Hampshire; NJ, New Jersey; NL, Netherlands; NM, New Mexico; NS, Nova Scotia; NSW, New South Wales; NT, Northern Territory; NV, Nevada; NVT, Nunavut; NWT, Northwest Territories; NY, New York; OH, Ohio; OK, Oklahoma; ONT, Ontario; OR, Oregon; PA, Pennsylvania; PEI, Prince Edward Island;PL, Poland; PT, Portugal; QUE, Quebec; QLD, Queensland; RI, Rhode Island; RO, Romania; SA, South Australia; SAS, Saskatchewan; SC, South Carolina; SD, South Dakota; SE, Sweden; SI, Slovenia; SK, Slovakia; TN, Tennessee; TX, Texas; UK, United Kingdom; UT, Utah; VA, Virginia; VIC, Victoria; VT, Vermont; WA, Western Australia; WAS, Washington; WV, West Virginia; WI, Wisconsin; WY, Wyoming; YT, Yukon.

higher IRs (≥5%) in the United Kingdom and EU countries, many of whom experienced a wave during this period (Supporting Information: Figure S1). The NNI estimates for the EU and UK showed a steep age gradient for severe illness (Figure 3) and critical illness (Figure 4) consistent with the steep age-risk gradient for SARS-CoV-2.[2,16] The NNI estimates were higher for critical illness versus severe illness given that the ICRs were generally lower than the ISRs (Supporting Information: Table S2). The same patten was observed for Israel (Supporting Information: Figures S10-12), Canada (Supporting Information: Figures S13-15), Australia (Supporting Information: S16-S18), and across the US (Supporting Information: Figures S19-S30). These estimates are helpful because they show a key property of the NNI using our estimation procedures: there is an inverse relationship between the NNI and IR. This pattern was repeated in the other regions we examined. Regions with IRs lower than the EU and UK during the fall 2021 had higher NNI estimates (e.g., Israel, Canada and Australia), whereas regions with IRs higher than the EU and UK had lower estimates (e.g., many US states).

4 | DISCUSSION

This study sought to outline a procedure for estimating the benefits of IMP using a novel variant of the NNT which we call the NNI. We used data from SARS-CoV-2 in various regions to demonstrate this procedure and its properties. The NNI and our estimation procedures have limitations.

First, we had to extrapolate from wild-type data to estimate the ARs for Delta infections in nonimmune individuals given that there was insufficient direct data. However, we were able to show that these extrapolations were consistent with existing data.

Second, there is also likely a degree of underestimation in the DRDC database of the IRs. It is difficult to accurately model underreporting rates and how they change over time because one is trying to model something where there are no data. This is shown by the extreme variation in underreporting estimates.[4,17] Local context/knowledge is required to estimate underreporting rates in a region over time, which isn't available on a global scale.

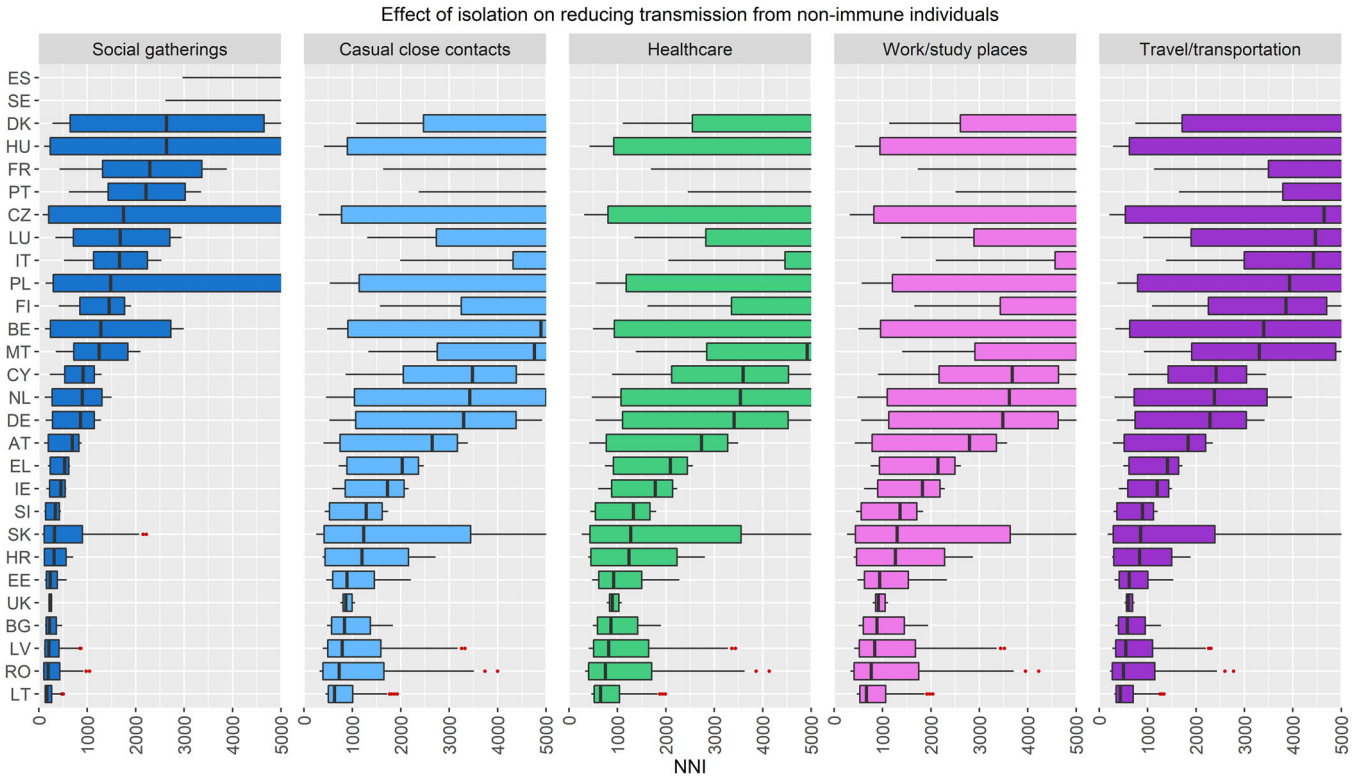

FIGURE 2 NNIs for transmission in nonhousehold settings in the European Union member states and United Kingdom. A region/setting with no box-and-whisker plot has an NNI > 5000 indicating a very low absolute risk reduction. AT, Austria; BE, Belgium; BG, Bulgaria; CY, Cyprus; CZ, Czechia; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, Netherlands; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom.

Third, the DRDC database provides population level IRs in each region over time, not an estimate of the IRs of sub-groups over time (immune vs. nonimmune). Therefore, the procedure assumes that the population-level IRs approximate the true IRs of nonimmune individuals in those regions during the period of interest. This assumption was necessary because, to the best of our knowledge, there are no SARS-CoV-2 databases which parse IRs by immunity. Moreover, any effort to estimate such IRs will be plagued with inaccuracies and uncertainties because doing so requires modelling extremely complex human interactions over time, which inevitably involves making many debatable assumptions about numerous dynamically interacting variables. Therefore, while they are approximations, we believe that the population-level IRs are reasonable approximations given the computational complexity of parsing IRs by immunity.

Fourth, the estimates for nonhousehold transmission are only for the first generation of spread, not subsequent generations. The exponential spread of transmission is not incorporated into the NNI estimation procedures because the NNI is estimated from SARs. Our procedures are restricted to the first generation of spread for the same reasons we did not try to estimate IRs by immunity. Any attempt to estimate the risks of >1 generation of spread will be plagued with inaccuracies and uncertainties because of the computational complexity of the problem. Therefore, rather than create the illusion of knowledge by generating questionable estimates of extremely complex phenomena, we opted for a simple procedure using empirically derived parameters which are based on only a few explicit assumptions.

Fifth, some of the known limitations of the NNT extend to the NNI.[18] The NNT is time-dependent since cumulative risks depend on the duration of follow-up. However, the NNT is often reported without the time window over which it was calculated. The time window is necessary for interpreting the NNT (e.g., an NNT of 10 over 3 months is not the same as an NNT of 10 over 3 years). For reasons detailed below, we believe that the NNI is best calculated using point-prevalence data, which means its time window is 1 day. Therefore, our NNI estimates are reported with the time window. The NNT is also often reported without stating the comparator (e.g., no treatment, placebo, established treatment, etc.), which is necessary to interpret the meaning of any outcome measure. The comparator for the NNI is essentially equivalent to 'no treatment' (i.e., nonimmune individuals in a region are freely able to access nonhousehold settings and the general community). The NNT is also usually rounded which can obscure differences between treatments. We believe rounding the NNI is appropriate because the general range is more important than precision since the main purpose of the NNI is to answer a key question about IMP: do we need to isolate just a few or many hundreds or thousands of nonimmune individuals in a

FIGURE 3 NNIs for severe illness in the European Union member states and United Kingdom. A region/age-group with no box-and-whisker plot has an NNI > 5000 indicating a very low absolute risk reduction. AT, Austria; BE, Belgium; BG, Bulgaria, CY, Cyprus; CZ, Czechia; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland, IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, Netherlands; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom.

region from accessing various settings to prevent nonhousehold transmissions and cases of severe/critical illness?

We now turn to four considerations about how to interpret the NNI which need to be made explicit. First, what is a 'high' versus 'low' NNI is open to debate at this moment. That judgement depends on how severe the outcome averted is and how costly (time, energy, resources, etc.) the IMP is, including the cost to the nonimmune individuals who are being isolated (unemployment, stigmatisation, restriction of liberties, etc.). We can look to the general medical literature on the NNT to help interpret the NNI. For example, the NNTs of acetylsalicylic acid for primary prevention of cardiovascular disease outcomes are ≥250, which are considered high NNTs.[19] However these comparisons are imperfect due to differences in outcome and time windows. The NNT is primarily concerned with within-individual outcomes (e.g., myocardial infarction), whereas the NNI for non-household transmission concerns a between-individual outcome where one or more other individuals may be impacted (i.e., transmission event). Furthermore, the ARR in the denominator of the NNI is based on point-prevalence, such that the risk is circumscribed over 1 day. The ARRs in the denominator of many NNTs are often based on incidence proportions and pertain to risks over months and years.

Second, the NNI estimates for the various types of nonhousehold settings (social gatherings, healthcare, etc.) can be viewed as the NNIs for preventing transmission events in settings of various intensities of contact. This is because the primary driver of a SAR is the intensity of contact (proximity, physical space, duration of contact, use of precautions, etc.). Stated differently, the types of settings can be viewed as proxies for intensity of contact, with household settings being the most intense which is why they have the highest SARs (Supporting Information: Table S1). For example, the SAR for 'social gatherings' can be viewed as the SAR one would typically see in a setting where people are gathered in close physical proximity in a closed physical space without precautions for a nontrivial duration of time but less than a household. This means it is possible that, for instance, a work setting could at times resemble what we are labelling a 'social gathering' (e.g., a lunch break, team meeting). The label matters less than the underlying contact intensity it is referring to.

Third, it is likely that we have underestimated the NNIs for severe/critical illness. This is because we used ISRs and ICRs from Herrera-Esposito and de los Campos[14] which are based primarily on the seroprevalence studies identified by Levin et al.[20] Pezzullo et al.[16] have suggested that these studies lead to inflated infection fatality rate (IFR) estimates due to a number of biases. This is consistent with the fact that the age-stratified IFRs in Herrera-Esposito and de los Campos[14] are two to threefold higher than the more complete analysis by Pezzullo et al.[16] Relatedly, the hospitalisation and ICU

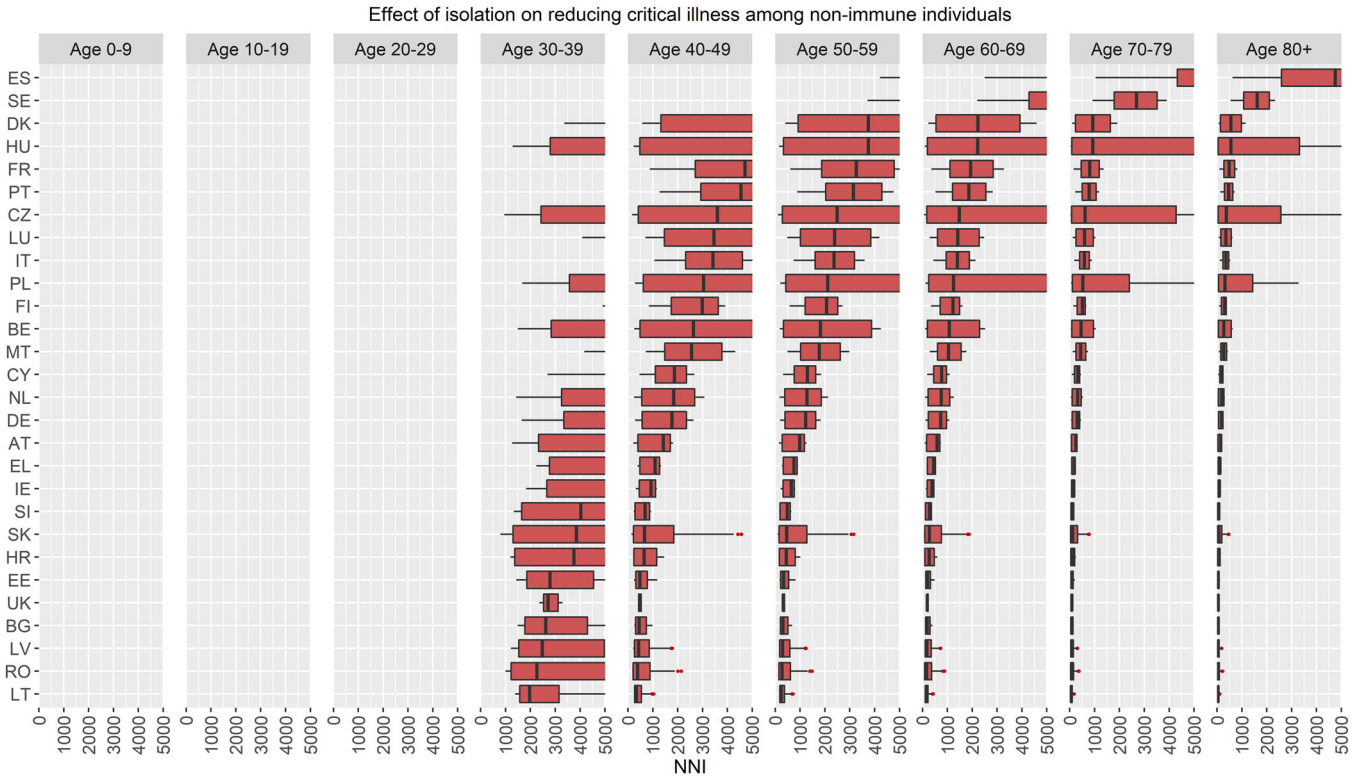

FIGURE 4 NNIs for critical illness in the European Union member states and United Kingdom. A region/age-group with no box-and-whisker plot has an NNI > 5000 indicating a very low absolute risk reduction. AT, Austria; BE, Belgium; BG, Bulgaria, CY, Cyprus; CZ, Czechia; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland, IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, Netherlands; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom.

data in Herrera-Esposito and de los Campos[14] come from early-to-mid 2020. Pezzullo et al.[16] note that this was a period when more people may have been admitted to hospital based on the precautionary principle from the common perception early in the pandemic of a high IFR. This may explain why the wild-type ISRs and ICRs we used to estimate the NNIs are implausibly high for many age groups (Supporting Information: Table S2). For instance, in the 60–69 age group, the ISR was almost 10% and the ICR was about 3%. These estimates are even higher after correcting for the Delta variant. Therefore, it is likely that these ISRs and ICRs are inflated by at least a factor of 2 to 3. However, to the best of our knowledge, these are the only age-stratified ISRs and ICRs available from the period when immunity was low and there is no simple means to statistically correct for these biases without introducing more assumptions into our procedures, which we want to minimise. The implication of this discussion is that our age-stratified NNIs for severe/critical illness are likely underestimates since inflated ISRs and ICRs will artificially lower the NNI.

Fourth, it is reasonable to ask why we did not use a risk metric to estimate the IR which uses a longer period of time (e.g., incidence proportion, period prevalence) since longer time windows would increase the IRs and thus lower the NNIs. Point-prevalence is the more appropriate metric for IR than incidence proportion and period prevalence for four reasons. First, the infection risk depends not just on new cases, but existing ones too. Second, incidence proportion and period prevalence depend on the time at risk. In general, shorter time windows will lower these metrics than longer time windows. If a time window is long enough, a cumulative risk can be high even if the risk on each day is low. However, there is no nonarbitrary way to set the time window to define the 'correct' time at risk. Time at risk is not an issue for point-prevalence because it is always a cross-section in time (the risk on a given day). Third, while risk over time is important, public health officials and communities are primarily concerned about the *current* risk of infection (i.e., point-prevalence), not, for example, the risk over the past 3 months. This was a retrospective study of September to November 2021, such that one could have taken the period prevalence of infectious cases during this time window to define the IRs. While this is not statistically incorrect to do, defining time at risk remains an issue. More importantly, period prevalence does not capture the risks that were known in the fall 2021 since, by definition, period prevalence is a retrospective measure (i.e., it is only known after the fact). Point-prevalence is known prospectively because it is a risk which can be measured on any given day. Fourth, one could counter by pointing out that one can use forecasted risks to prospectively estimate IRs over longer time windows than 1 day. However, forecasted risks are not clearly preferable to point-prevalence. Time at risk issues remain a concern since one must select a time window for the forecast. Inaccuracy and uncertainty of

forecasts is also a major challenge for any predictive model of infectious disease dynamics. This is because of the multifactorial/interacting nature of these dynamics and uncertainty in selecting/estimating the relevant predictors. Moreover, one cannot prospectively know if a forecasted IR is accurate since this, by definition, is discovered only retrospectively, which defeats the purpose of using forecasts to estimate NNIs. Relatedly, using period prevalence over a retrospective time window to forecast what the IR will be over the next months or years is challenging since it assumes the future will correspond to the past. The SARS-CoV-2 pandemic has shown that this was a tenuous assumption except over short periods of time. For these reasons, forecasted IRs are often more a form of speculation with wide uncertainty intervals than actually measurable risks. Acknowledging these nuances and their impact on how to interpret the NNI, point-prevalence is the more appropriate metric of IR to estimate NNIs. The advantage is that point-prevalence is an actually measurable risk which can be known prospectively and does not suffer from time at risk issues. The disadvantage is that it does not quantify future risks or risks over longer periods of time.

Notwithstanding these limitations and considerations, our procedures show that the NNI can be estimated easily from epidemiological metrics commonly used to understand viral illnesses (e.g., prevalence, SARs, hospitalisation rates, etc). When these parameters are based on the risks of nonimmune individuals, they yield estimates of the ARs of nonhousehold transmission and severe/critical illness in nonimmune individuals. The reciprocal of these ARs generates estimates of how many nonimmune individuals need to be isolated using IMP to achieve the purported benefits on nonhousehold transmission and severe/critical illness. Our study shows the utility of the NNI, which is a simple and intuitive measure to quantify the benefits of IMP. The NNI can be estimated for any virus and at any scale (e.g., medical wards, long-term care facilities, municipalities, etc.), as long as you (i) have estimates of the IRs in the area-of-interest and (ii) have information about transmission (SARs) and severity (ISRs and ICRs) in nonimmune individuals for the circulating variant(s) in that area. One can also calculate the NNI for preventing death from a viral illness by using age-stratified IFRs in the denominator rather than ISRs or ICRs.

We believe a tentative observation about the NNI estimates is worth making. While not every region we examined in our worked example implemented IMPs during the fall 2021, some did with differing degrees of intensity (e.g., UK, EU states, Canada, Australia and Israel). For many of these regions, the NNI estimates suggest that one would have needed to prevent hundreds and sometimes thousands of nonimmune individuals from accessing various settings (e.g., places of leisure, working in healthcare, etc) on any given day to prevent one transmission event or one case of severe/critical illness. It is critical to underscore that these findings don't generalize to other regions and/or time periods of the SARS-CoV-2 pandemic. We cannot know if these findings apply under new conditions. This is because risks of infection, transmission, and severe/critical illness change over time and space since these risks depend on many factors. Nevertheless, these estimates may have implications for a cost–benefit analysis of IMP in these regions.

AUTHOR CONTRIBUTIONS

Aaron Prosser, Bartosz Helfer and David L. Streiner contributed equally to this work. Aaron Prosser, Bartosz Helfer and David L. Streiner conceived the idea. Aaron Prosser and Bartosz Helfer acquired the data, screened records, and extracted data. Aaron Prosser and Bartosz Helfer performed the formal analysis. Aaron Prosser, Bartosz Helfer and David L. Streiner wrote the first draft of the manuscript. All authors gave critical feedback on the revised report and approved the final version of the manuscript. The corresponding author attests all listed authors meet authorship criteria and that no others meeting criteria have been omitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript/Supporting Information Material and at https://github.com/TheNNIforViralTransmission/SARS-CoV-2 and https://decision-support-tools.com/map

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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