HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2022 February 23.

Published in final edited form as:

Vaccine. 2019 May 27; 37(24): 3229–3233. doi:10.1016/j.vaccine.2019.04.065.

Effect of propensity of seeking medical care on the bias of the estimated effectiveness of rotavirus vaccines from studies using a test-negative case-control design

Michael Haber[a,*], **Benjamin A. Lopman**[b,c], **Jacqueline E. Tate**[c], **Meng Shi**[a], **Umesh D. Parashar**[c]

[a] Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA, USA

[b] Department of Epidemiology, Emory University, Atlanta, GA, USA

[c] Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

Background: Rotavirus is the leading cause of severe diarrhea among children worldwide, and vaccines can reduce morbidity and mortality by 50–98%. The test-negative control (TNC) study design is increasingly used for evaluating the effectiveness of vaccines against rotavirus and other vaccine-preventable diseases. In this study design, symptomatic patients who seek medical care are tested for the pathogen of interest. Those who test positive (negative) are classified as cases (controls).

Methods: We use a probability model to evaluate the bias of estimates of rotavirus vaccine effectiveness (VE) against rotavirus diarrhea resulting in hospitalization in the presence of possible confounding and selection biases due to differences in the propensity of seeking medical care (PSMC) between vaccinated and unvaccinated children.

Results: The TNC-based VE estimate corrects for confounding bias when the confounder's effects on the probabilities of rotavirus and non-rotavirus related hospitalizations are equal. If this condition is not met, then the estimated VE may be substantially biased. The bias is more severe in low-income countries, where VE is known to be lower. Under our model, differences in PSMC between vaccinated and unvaccinated children do not result in selection bias when the TNC study design is used.

Conclusions: In practice, one can expect the association of PSMC (or other potential confounders) with the probabilities of rotavirus and non-rotavirus related hospitalization to be similar, in which case the confounding effects will only result in small bias in the VE estimate from TNC studies. The results of this work, along with those of our previous paper, confirm the TNC design can be expected to provide reliable estimates of rotavirus VE in both high- and low-income countries.

* Corresponding author. mhaber@emory.edu (M. Haber).

Conflict of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.065.

Keywords

Rotavirus vaccines; Test-negative design; Vaccine effectiveness; Confounding bias; Selection bias; Probability models

1. Introduction

Rotavirus is the leading cause of severe diarrhea among children worldwide and was estimated to cause 215,000 childhood deaths in 2013 [1]. Two vaccines against rotavirus were licensed for use in 2006 to reduce the burden of rotavirus diarrhea (RD). In randomized clinical trials, the efficacy of these vaccines against RD ranged from 85%–98% to 50%–64% in high and low income settings, respectively [2]. Factors such as interference by concurrent enteric infections, malnutrition, high levels of maternal antibody, and interference with concurrently administered oral polio vaccine may adversely affect the performance of these vaccines in low-income settings. Due to this variable performance of rotavirus vaccines in clinical trials, evaluations of vaccine effectiveness (VE) in routine use in a diverse range of settings are a public health priority.

Further, randomized placebo-controlled clinical trials to evaluate rotavirus VE are challenging to conduct, as vaccination against rotavirus is now recommended globally. Therefore, observational studies based on patients seeking care or hospitalized for RD are the best options for obtaining estimates of rotavirus VE. Case-control studies are most commonly used for this purpose. In these studies, the odds of vaccination are compared between individuals who contracted RD (cases) and control individuals. Controls should be representative of the source population that produces the cases.

Over the past decade, a new type of case-control study to evaluate field effectiveness of vaccines has evolved. In these test-negative control (TNC) studies, individuals seeking care or hospitalized for clinical symptoms like those of the cases of illness caused by the pathogen of interest, but who test negative for that pathogen, serve as controls. Receipt of the vaccination of interest is compared between cases and the test-negative controls. TNC studies have mainly been used to estimate influenza VE [3–5], but they are also being used to estimate VE against other diseases, including rotavirus diarrhea (RD) [2,6,7]. TNC studies are expected to reduce the bias of VE estimates because cases and controls have similar symptoms and therefore assumed to have similar care-seeking behaviors and may also be similar with respect to other potential confounders, such as age, health, or access to health care. Also, since case or control status is not known until testing results are obtained, bias in ascertainment of vaccination status can be avoided. Such studies are also logistically easier and more economical to conduct, as no external control group needs to be recruited.

In an earlier paper [7], we investigated the effects of two sources of bias on TNC-based estimates of rotavirus VE against RD resulting in hospitalization: (a) misclassification bias resulting from errors in the test for rotavirus infection (false positives or false negatives), and (b) bias associated with the possible effect of rotavirus vaccination on the probability of non-rotavirus diarrhea (NRD). We concluded that although these sources could result in

substantial bias under certain conditions, it is likely that the effects on the bias of rotavirus VE estimates will be minimal in most realistic scenarios.

In this work, we focus on biases of TNC-based VE estimates resulting from differences between vaccinated and unvaccinated children with respect to their propensity of seeking medical care (PSMC). PSMC may be associated with the likelihood of a child being vaccinated. Plus, independent of vaccination, PSMC may be associated with the child's probabilities of developing diarrhea and of being hospitalized if s/he suffers from diarrhea.

2. Methods

We adapt a probability model developed by Shi et al. [8] to evaluate the bias of estimates of influenza VE from TNC (and other) studies. In our model, each child is assigned a binary covariate corresponding to her/his PSMC status (high or low). A preset proportion of the children are considered vaccinated. The probability of vaccination may depend on the child's PSMC, and we assume that a child's vaccination status does not change during the study. A child may develop diarrhea resulting either from rotavirus (RD) or from another pathogen (NRD). The probabilities of these outcomes may depend on the child's vaccination status and PSMC status. A child with diarrhea may be hospitalized. The probabilities of hospitalization may depend on the child's PSMC status and the type of diarrhea (RD or NRD). Children hospitalized because of diarrhea are tested for rotavirus infection. Children who test positive serve as cases while those testing negative become controls. We assume that the test's sensitivity and specificity do not depend on the child's vaccination status or other characteristics. A Directed Acyclic Graph (DAG) of the model is presented in Fig. 1.

Our model includes the following parameters: The probability of being classified as 'high' or 'low' PSMC, the probability of being vaccinated for each level of PSMC, the probabilities of RD and NRD among vaccinated and unvaccinated children for each level of PSMC, and the probabilities of being hospitalized given a child's PSMC and type of diarrhea (RD or NRD). We make the following simplifying assumptions: (1) the diagnostic test's sensitivity and specificity are 100%, (2) vaccination does not directly affect the probability of NRD (this is the fundamental assumption underlying the TNC design [3]), (3) VE does not depend on PSMC, and (4) the probability of hospitalization given the child's PSMC does not depend on her/his vaccination status. We consider two scenarios for the values of these parameters: Scenario H represents a high-income setting where incidence of RD is relatively low and VE is relatively high, such as the U.S., while scenario L represents a low-income, setting such as sub-Saharan Africa, where incidence of RD is comparatively high and VE is moderate.

We use the following technique to reduce the number of input values that must be assigned to the probabilities mentioned above: We first define a 'reference' child as an unvaccinated child with low PSMC. We then assign input values to the probabilities of a reference child. The probabilities of all other children can be determined from the probabilities of a reference child and the values of a few risk ratios (RR's).

Table 1 presents the values assigned to the model's parameters (probabilities) under each of the scenarios. We assumed that each child is assigned an unobservable numeric PSMC score.

A child's PSMC status is defined as 'high' or 'low' if her/his PSMC score is above or below the median PSMC score in the study population, respectively. Therefore, we can assume, without loss of generality, that the probability of high/low PSMC is 0.5. The remaining values in Table 1 are from our earlier paper [7]. Table 2 defines the RR's that are used to calculate probabilities of non-reference children and their values or ranges. The first RR in Table 2 compares the probability of RD in vaccinated and unvaccinated children. Then the true VE is [1 – RR(RD|Vacc)] × 100%. We set the true VE to 90% in scenario H and 50% in scenario L. The second and third RR's in Table 2 represent the effect of high PSMC on the probabilities of RD and NRD, respectively. The fourth RR compares children with high and low PSMC with respect to their probability of hospitalization if they have diarrhea.

We now present three examples of calculation of probabilities of non-reference children:

1. The probability of NRD of an unvaccinated child with high PSMC equals the probability of NRD of an unvaccinated child with a low PSMC (a reference child) multiplied by RR(NRD|HPSMC).
2. The probability of RD of a vaccinated child with high PSMC equals the probability of RD of an unvaccinated child with low PSMC (a reference child) multiplied by RR(RD|Vacc) and by RR(RD|HPSMC).
3. The probability that a child with high PSMC is hospitalized equals the probability of a child with low PSMC multiplied by RR(Hosp|HPSMC).

We developed a SAS program that uses the values of the input parameters (Table 1) and the risk ratios (Table 2) to calculate the probabilities that a randomly selected child is classified as either a vaccinated case, vaccinated control, unvaccinated case or unvaccinated control. The expected value of the VE estimate is calculated as 100% times one minus the ratio of the odds of being vaccinated in cases and in controls. The bias of an estimate is the difference between the expected estimated VE and the true VE. Details of the calculations are described in Shi et al. [8]. The SAS program for calculating the bias under our model can be found in the Supplement.

2.1. Potential sources of bias

As stated in the introduction, the objective of this work is to evaluate the effects on the bias of the VE estimate of differences in PSMC between vaccinated and unvaccinated children. Table 3 lists various factors resulting from these differences that may bias the estimates. Each of these factors corresponds to the deviation of one of the RR's defined in Table 2 from its null value of 1.0.

Factors A1 and A2 may result in confounding biases due to the association of PSMC with the probabilities of vaccination and the outcomes that defines cases and controls, respectively. We conducted Monte Carlo simulations to explore the joint effect of factors A1 and A2 on the bias of VE estimates. In these simulations, each of the corresponding risk ratios (see Table 3) was assigned an independent uniform distribution between 0.5 and 2.0. Factor A3 reflects a situation where PSMC is associated with the probabilities of both outcomes but the RR's corresponding to the modification of the probabilities of both outcomes are the same. Factor B may result in selection bias due to the association of PSMC

with the probability that a child with diarrhea is hospitalized and is therefore included in the TNC study.

3. Results

When none of the potential sources of bias listed in Table 3 is present then the VE estimate derived from a TNC study is unbiased. The bias is zero even though we use the odds ratio to estimate a risk ratio. This property of the TNC-based estimate of VE does not rely on the 'rare disease' assumption [8].

3.1. Factors A1 and A2

Fig. 2 presents the joint effect of factors A1 and A2 for each scenario. For example, under Scenario L, when the probability of RD in a child with high PSMC is one-half that of the corresponding probability in a child with low PSMC (i.e., RR(RD|HPSMC) = 0.5), and the probability of NRD of a child with high PSMC is 50% higher than that of a child with low PSMC (RR(NRD|HPSMC) = 1.5), then the expected estimated VE is 69% while the true VE is 50%. In general, the bias of VE estimates is smaller in Scenario H compared to Scenario L because the true VE in Scenario H is much closer to 100%. We also learn from Fig. 2 that the bias increases as the absolute value of the difference between the RR's that define factors A1 and A2 increases.

We conducted Monte Carlo simulations to further explore the joint effect of factors A1 and A2 on the bias of VE estimates. We used the median absolute value of the bias (AVB) as a measure of the overall magnitude of the bias. The AVB is the difference between the estimated and the true VE when the sign is ignored. For example, when the true VE is 50% and the estimated VE is 45% then ABV = 5 percentage points. We found that when both risk ratios defining factors A1 and A2 varied from 0.5 to 2.0, then the median ABV was 0.8 percentage points in scenario H and 4.1 percentage points in Scenario L. In other words, when only factors A1 and A2 may affect the bias of the VE estimate then in Scenario H the estimated VE is, on average, about one percentage point higher or lower than the true VE, which may be considered minimal bias. In scenario H the estimated VE is, on average, about 4 percentage points higher or lower than the true VE, which can be considered small to moderate bias.

3.2. Factor A3

From Fig. 2 it is easy to see that when PSMC is associated with the probabilities of both RD and NRD such that the RR's comparing the probabilities of diarrhea in children with high and low PSMC are the same for rotavirus and non-rotavirus diarrhea, then the VE estimate from a TNC study is unbiased.

3.3. Factor B

We found that association between PSMC and the probabilities of being hospitalized because of diarrhea does not bias the VE estimate. This can be attributed to our assumption the vaccination is not directly associated with the probability of hospitalization.

The unbiasedness properties associated with factors A3 and B can be shown to hold in general for VE estimates from test-negative designs. Mathematical proofs can be found in Shi et al. [8].

4. Discussion

One of the arguments in favor of the test-negative case-control design is reducing bias resulting from differences between vaccinated and unvaccinated individuals regarding their care-seeking behaviors. We used a probability model [8] to verify this property of the TNC design in the context of a study to estimate rotavirus VE against hospitalization resulting from diarrhea. We found that differences in vaccination coverage between individuals with high and low PSMC will not result in a large bias in estimated VE as long as the confounding effects of PSMC on rotavirus and non-rotavirus diarrhea, i.e., RR(RD|HPSMC) and RR(NRD|HPSMC) are similar. While it may be difficult to test this condition (as it is difficult to measure person's propensity of seeking medical care), it makes sense to assume that the association of PSMC (or other potential covariates) with the probability of diarrhea is similar for RD and NRD.

We made the following assumptions in our calculations of VE bias: (1) the diagnostic test's sensitivity and specificity are 100%, (2) vaccination does not directly affect the probability of NRD (this is the fundamental assumption underlying the TNC design [3]), (3) VE does not depend on PSMC, and (4) the probability of hospitalization given the child's PSMC does not depend on her/his vaccination status. We studied the effects of violation of the first two assumptions in our earlier paper [7] and concluded that in most real-life settings these violations are expected to be minor and are not likely to increase the bias of rotavirus VE estimates from TNC studies. The remaining two assumptions look reasonable, though it may be difficult to verify them.

To explore the impact of the choice of the values of the probabilities listed in Table 1, namely the probabilities of vaccination, developing RD, NRD, and hospitalization, we conducted a series of sensitivity analyses. Since we found that under our assumptions, only factors A1 and A2 may bias the VE estimate, we repeated the Monte-Carlo simulations described above to explore the effects of these factors with different values of the probabilities in Table 1. We refer to the values of the probabilities in Table 1 as the 'baseline values'. We found that as long as the difference between probabilities of being vaccinated between children with low and high PSMC remained fixed (0.3), changes in the values of the other probabilities had very little effect on the bias of VE estimates. With the baseline values of the probabilities in Table 1, the median absolute value of the bias (AVB) was 0.8 percentage points in scenario H and 4.1 percentage points in Scenario L. With different values of these probabilities, the median AVB in scenario H ranged between 0.6 and 0.9 percentage points, while the median AVB in Scenario L ranged between 3.0 and 4.4 percentage points. Hence, choice of different values for the probabilities in Table 1 is not expected to result in big changes of the VE bias resulting from factors A1 and A2. As stated in the Methods section, we classify a person as 'high PSMC' if her/his unobserved PSMC score exceeds the median of that score in the study population. Therefore, we kept the probability of high PSMC fixes at 0.5. Since rotavirus vaccine coverage is high (around

80%) in most populations [9], it makes sense to assume that the difference in vaccine coverage between individuals with low and high PSMC will not be much larger than 0.3. A substantially smaller (larger) difference would decrease (increase) the bias, as this would decrease (increase) the association between the covariate and the probability of vaccination.

From a broader perspective, our results still apply if we replace PSMC with any covariate that is associated with (1) the probability of being vaccinated, (2) the probability of developing rotavirus and non-rotavirus diarrhea, and (3) the probability of being included in the study. Therefore, one would expect such a covariate to induce both confounding and selection bias. We found that under our model, the test-negative design properly controls the selection bias. However, confounding bias may still exist unless the associations of the covariate with the probabilities of developing RD and NRD are similar. A recent paper [10] discusses the impact of selection bias on VE estimates from TNC studies. The model used in that paper is not equivalent to our model as in their model, PSMC is not directly associated with the probabilities of illness.

5. Conclusion

The results of this study along with those of our previous study [7] confirm the notion that the test-negative design can be expected to provide reliable estimates of rotavirus VE in the setting considered here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This work was supported by the Centers for Disease Controls and Prevention (CDC) via an IPA [181PA1812107]. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

[1]. Tate JE. Burton AH, Boschi-Pinto C, Parashar UD. Global, regional, and national estimates of rotavirus mortality in children < 5 years of age, 2000–2013. Clin Infect Dis 2016;62(Suppl 2):S96–S105. [PubMed: 27059362]

[2]. Tate JE, Patel MM, Cortese MM, Payne DC, Lopman BA, Yen C, et al. Use of patients with diarrhea who test negative for rotavirus as controls to estimate rotavirus vaccine effectiveness trough case-control studies. Clin Infect Dis 2016;62(S2):S106–14. [PubMed: 27059343]

[3]. Skowronski DM, Masaro C, Kwindt TL, Mak A, Petrie M, Li Y, et al. Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel network: results from the 2005–2006 season of dual A and B vaccine mismatch in Canada. Vaccine 2007;25:2842–51. [PubMed: 17081662]

[4]. Sullivan SG, Shuo F, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Exp Rev Vacc 2014;13:1571–91.

[5]. Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis 2016;16:942–51. [PubMed: 27061888]

[6]. Schwartz LM, Halloran ME, Rowhani-Rahbar A, Neuzil KM, Victor JC. Rotavirus vaccine effectiveness in low-income settings: an evaluation of the test-negative design. Vaccine 2017;35:184–90. [PubMed: 27876198]

[7]. Haber M, Lopman BA, Tate JE, Shi M, Parashar UD. A comparison of the test-negative and traditional case-control study designs with respect to the bias of estimates of rotavirus vaccine effectiveness. Vaccine 2018;36:5071–6. [PubMed: 29980389]

[8]. Shi M, An Q, Ainslie KEC, Haber M, Orenstein WA. A comparison of the test-negative and the traditional case-control study designs for estimation of influenza vaccine effectiveness under nonrandom vaccination. BMC Infect Dis 2017;17:757. [PubMed: 29216845]

[9]. Mwenda JM, Burke RM, Shaba K, Mihigo R, Tevi-Benissan MC, Mumba M, et al. Implementation of rotavirus surveillance and vaccine introduction - World Health Organization African Region, 2007–2016. Morbid Mortal Week Rep (MMWR) 2017;66:1192–6.

[10]. Jackson ML, Phillips CH, Benoit J, Kiniry E, Madziwa L, Nelson JC, et al. The impact of selection bias on vaccine effectiveness estimates from test-negative studies. Vaccine 2018;36:751–7. [PubMed: 29254838]

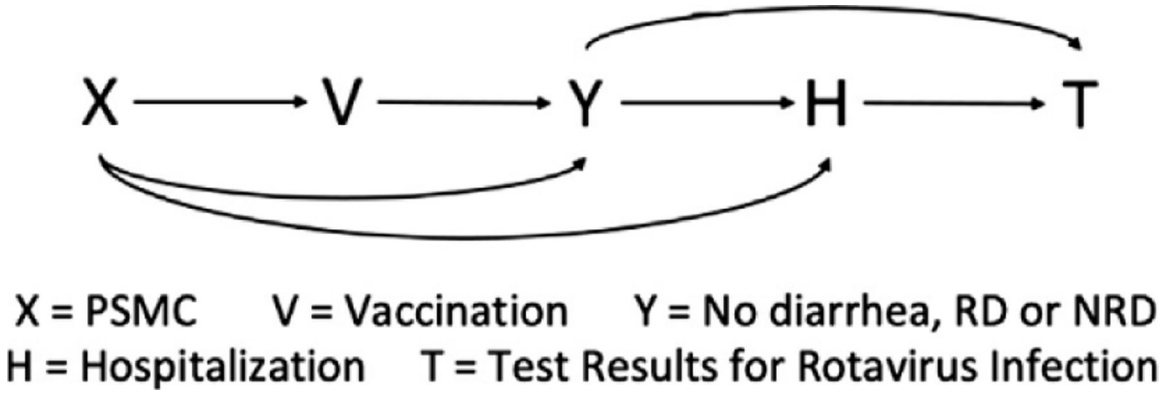

Fig. 1.
Directed Acyclic Graph (DAG) of the model.

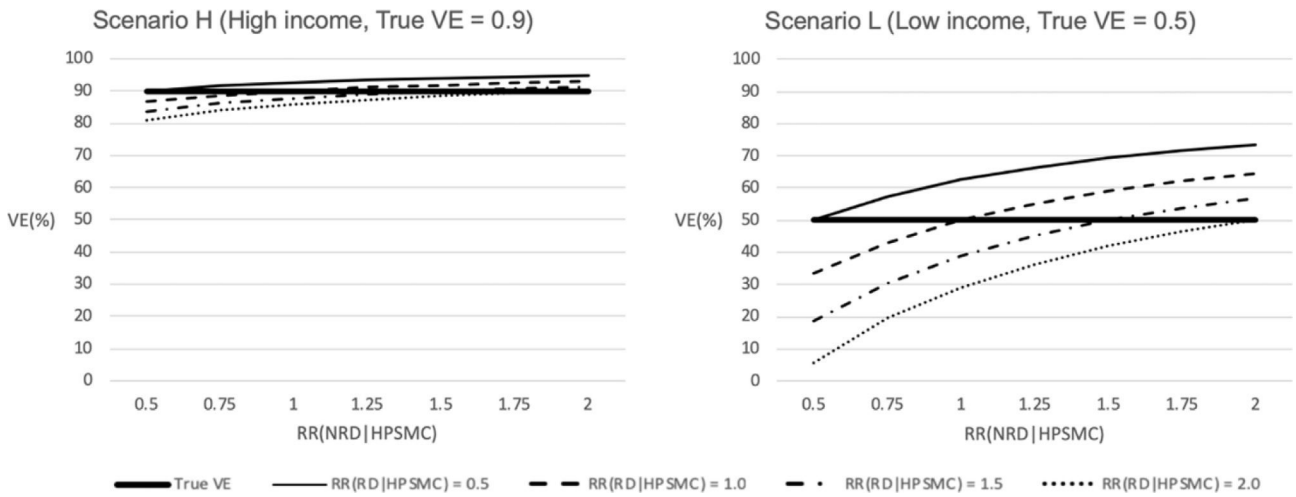

Fig. 2.
Expected VE Estimates under Biases A1 and A2.

Table 1

Probabilities of various events under two scenarios: Scenario H corresponds to a high-income country and Scenario L to a low-income country.

Probability	Scenario H	Scenario L
Probability of high PSMC	0.5	0.5
Probability of being vaccinated for a child with low PSMC	0.65	0.65
Probability of being vaccinated for a child with high PSMC	0.95	0.95
Probability of RD for an unvaccinated child with low PSMC	0.01	0.06
Probability of NRD for a unvaccinated child with low PSMC	0.03	0.19
Probability of hospitalization for a diarrhea patient with low PSMC	0.4	0.4

Table 2

Risk ratios comparing a non-reference and a reference child.

Risk ratio (RR)	Notation	Value or range
Ratio of probabilities of RD in vaccinated and unvaccinated children	RR(RD|Vacc)	1–VE = 0.1 (10%) in scn H or 0.5 (50%) in scn L
Ratio of probabilities of RD in children with high and low PSMC	RR(RD|HPSMC)	0.5–2.0
Ratio of probabilities of NRD in children with high and low PSMC	RR(NRD|HPSMC)	0.5–2.0
Ratio of probabilities of hospitalization in children with high and low PSMC	RR(Hosp|HPSMC)	0.5–2.0

Vacc = vaccination, HPSMC = high PSMC, Hosp = hospitalization.

A reference child is unvaccinated and is classified as low PSMC.

Table 3

Potential sources of bias and the corresponding risk ratios.

Label	Factor (potential source of bias)	RR	Range
A1	Probability of RD is associated with PSMC	RR(RD|HPSMC)	0.5–2.0
A2	Probability of NRD is associated with PSMC	RR(NRD|HPSMC)	0.5–2.0
A3	Probabilities of RD and NRD are associated with PSMC and the RR's are equal	RR(RD|HPSMC) = RR(NRD|HPSMC)	0.5–2.0
B	Probability of hospitalization (due to RD or NRD) is associated with PSMC	RR(Hosp|HPSMC)	0.5–2.0