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A Standardized Method to Calculate the Number Needed to Vaccinate

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Degree to be awarded: MPH

Global Health, Infectious Disease

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A Standardized Method to Calculate the Number Needed to Vaccinate

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An abstract of A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Global Health 2018

Abstract

A Standardized Method to Calculate the Number Needed to Vaccinate

By Kanya Rajagopalan

INTRODUCTION: There are many methods to calculate the Number Needed to Vaccinate (NNV). These methods range from modeling to using standardized formulas derived from the Number Needed to Treat. Due to the variety of methods used to calculate and interpret the NNV, there is no comparability between methods to inform global interventions.

METHODS: This systemic literature review details the different methods and interpretations of the NNV to determine whether a standardized method to calculate the NNV can be derived. A total of 37 articles were selected for review from which data regarding calculation method, interpretation, NNV, and advantages/disadvantages of each method were extracted.

RESULTS: The method that met the most criteria for that of a standardized method was 1/Attributable Risk Ratio/Length of Study Period. This is because this method was simple, used data that was easily available, and accounted for long-term effects of vaccination, such as vaccine waning. There was no method that had been used that accounted for indirect effects of vaccination without compromising on generalizability.

CONCLUSION: A standardized method to calculate the NNV is important, as this can lead to data sharing and globally informed efforts to lower the burden of infectious disease.

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ACKNOWLEDGEMENTS:

My most sincere thanks and appreciation go to the following:

To Dr. Saad Omer, who is a leading expert in the field of vaccines and vaccine-related diseases and has been a great mentor throughout the course of this thesis project. The experience and practical skills that I gained through this experience will be critical assets in developing my future career goals.

To Dr. Natasha Crowcroft and Dr. Shelly Bolotin for being incredible collaborators and lending their international expertise, despite their busy schedules, to assist me in developing this document.

To Ms. Beryl Guterman for her constant encouragement, advice and support throughout this whole process.

To Ms. Emily Chuba for her constant support and encouragement.

To Mom and Dad for always giving me the freedom to follow my dreams, encouraging me to work hard, and believing in me.

To my husband for putting up with me through this last year with patience, encouragement and emotional support and never letting me give up on myself.

And finally, to my family and friends at RSPH, who truly made this process so much easier.

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INTRODUCTION/RATIONALE:

The number needed to vaccinate (NNV) is a calculation that is used to interpret the number of people that need to be vaccinated to prevent one case of disease/hospitalization/death/adverse outcome. It is a very useful method that is used in a wide array of circumstances, the most common of which are to determine benefit of vaccination programs and to determine cost-effectiveness of these vaccination programs. Due to its simplicity and ability to be understood by a lay audience, it is one of the most effective methods to demonstrate the effect of vaccination programs[1]. The challenge with the NNV, however, is that there are many ways to calculate it, and it is therefore not comparable among studies.

A major challenge for estimating the number needed to vaccinate is the lack of standardized method to calculate and interpret it. Because of this, though region-specific interventions to lower infectious disease burden can be informed by NNV, global interventions cannot as the NNV is not comparable if the same methods are not used. For example, in a study by Rahman et al., the BCG vaccine for tuberculosis was proven to have no public health impact because the NNV was 2125-10,399[2]. In another study for a tuberculosis vaccine, however, it was said to have a public health impact with a NNV of 9000[3]. The two studies, however, used different methods, because of which the thresholds were different to determine at what point NNV supports a vaccination program. This happens quite frequently in literature, as can be seen in Table 1.

Table 1:

Research Question	Method	NNV	Does NNV support

			vaccine related policy-making?
Can influenza vaccination reduce influenza-attributable medical visits?[4]	1/Attributable Risk Reduction	4255-6927 (24-59 months) 1031-3050 (6-23 months)	Yes
Is the vaccine for IPD effective ?[5]	1/Attributable Risk Reduction	5206	Yes
Is the HPV vaccine cost effective?[6]	1/Attributable Risk Reduction	120	Yes
Is the cocoon program cost effective?[7]	1/Attributable Risk Reduction	10,000	No
Is post exposure prophylaxis for rabies feasible?[8]	1/Attributable Risk Reduction	314,000-2.7 million	No
Does the funding of meningococcal vaccines seem feasible?[9]	1/Attributable Risk Reduction	33,784-38,610	No
What is the NNV to prevent morbidity due to HPV?[10]	Cohort Model	324	Yes
What is NNV to	Cohort Model	11	Yes

prevent morbidity due to Herpes Zoster (HZ)?[11]			
Is TB vaccine cost effective?[3]	Other	9,000	Yes
Is the current BCG vaccine cost effective?[2]	Other	2125-10,399	No

There are many ways to calculate the NNV. It can be calculated via modeling (through Agent-Based Models, Markov Chain Monte Carlo (MCMC) Model Simulations, cohort models or Bayesian evidence synthesis approaches). It is also commonly calculated as 1/Attributable Risk Reduction (ARR), where ARR is the product of the annual incidence rate and vaccine effectiveness. Based on this method, 1/ARR/Study Length Period has also been used to calculate NNV. There are many other, less common methods that have all been used and advocated, which will not be discussed in detail in this systemic review.

There is a need for a standardized measure to calculate NNV. A standardized method to calculate the NNV is important not only in countries with high infectious disease burden, but especially in countries/regions with a low infectious disease burden as in these countries, the NNV is especially high and the magnitude of NNV affects decision-making. The NNV is a widely applicable measure that can be used to inform polices that will reduce this burden. It provides a community-based indication of the

effect of a vaccine, incorporating factors such as vaccine waning and outcomes in the community as a whole[12], and is thus more effective than measures such as vaccine efficacy in providing an estimate of the utility of a vaccine program.

An ideal method for calculating the NNV would:

1) Be simple to understand and intuitive[13]
2) Account for short-term/long-term effects of vaccination[14]
3) Account for indirect effects of vaccination[14]
4) Use information that was easily available

The purpose of this systemic review is to review the different methods to estimate NNV and determine whether a method can be selected, based on the above criteria, that is best suited as a standardized measure to calculate NNV .

METHODS

SEARCH STRATEGY:

A search was performed using the search terms “number” AND “needed” AND “to” AND “vaccinate” on Web of Science, EMBASE, CINAHL, and PubMed. Data that was extracted from the articles were research question, NNV, method to calculate NNV (or analysis of the NNV), and the discussion of the method used to calculate the NNV.

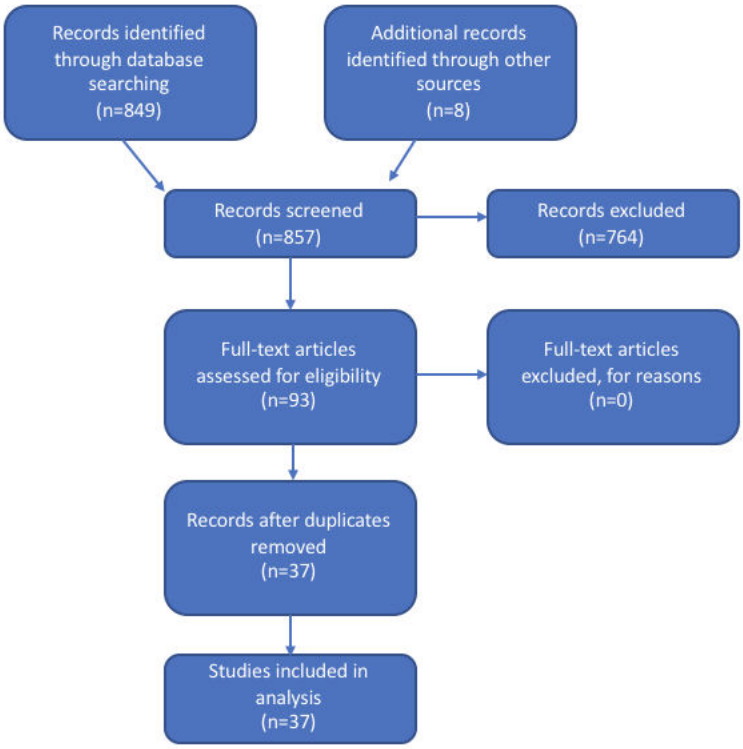
Table 2:

INCLUSION CRITERIA	EXCLUSION CRITERIA
Should interpret number needed to vaccinate	The full text was not available
Should either calculate NNV as a primary measure or analyze NNV	It was a meta-analysis that does not detail the methods
Should detail NNV calculation in methods if calculated	The study was done for non-humans
Should be in English	
Should include NNV in the title or abstract	

RESULTS OF SEARCH:

A total of 849 abstracts/titles were screened for the words "number needed to vaccinate" on Web of Science, EMBASE, CINAHL and PubMed. Of these, 37 references were used in this literature review.

Figure 1:



Study characteristics are summarized in Table 1.

Table 3:

CHARACTERISTICS OF STUDY RESULTS (N=37)	
Purpose of calculating NNV	
Assessed effectiveness of a vaccine	22

program	
Assessed public health importance of a vaccine	3
Assessed cost effectiveness of a vaccine program	12
Method of NNV calculation	
Method based on NNT	17
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RESULTS:

USE OF NNV:

The number needed to vaccinate has mainly been used to demonstrate feasibility of vaccination programs. Kelly et al. had determined feasibility of the vaccine program for invasive pneumococcal disease by using the NNV to compare vaccine costs for invasive pneumococcal disease to the costs for the influenza vaccine to prevent one death per year[5]. Lewis et al. also used the NNV to determine that the influenza vaccination program can reduce influenza-attributable medical visits in children by assessing the NNV to prevent one influenza-attributable medical visit[4].

NNV had also been used in systemic meta-analyses to measure the feasibility of vaccine programs. Jefferson et al. conducted a systemic review/meta-analysis to measure the feasibility of influenza vaccination programs in children, using NNV to compare prevention of laboratory confirmed influenza by live attenuated and inactivated vaccines[15]. NNV had also been used in a meta-analysis to determine whether RSV vaccine programs are feasible [16].

Finally, NNV had been multiplied by vaccine doses needed and vaccine cost to compare magnitude of resources needed for vaccination programs. In two studies by Meregaglia and Skowronski, it was concluded that the "cocooning" program, where parents were vaccinated to protect their baby from pertussis until the baby was old enough to be vaccinated, was not efficient and was extremely resource intensive, as the NNV was extremely high[7,17].

NNV has been used to support a national program for HPV vaccination[6], to advocate against post-exposure prophylaxis for rabies[8], to demonstrate that annual influenza vaccination is associated with a reduction in all-cause mortality rates[18], and to determine effectiveness of a vaccine program for Invasive Meningococcal Disease that has not yet been released[9]. Due to the broad range of uses of NNV, if there were a standardized method to calculate this measure, it could potentially be used in broad global recommendations as well as those that are region specific.

MODELING BASED METHODS TO CALCULATE NNV:

9 studies used modeling to demonstrate the benefit of a vaccine program. Out of these 9 studies, 2 used an agent-based dynamic model, 3 used a MCMC simulation model, 3 used a cohort model, and 1 used a Bayesian evidence synthesis approach.

Agent Based Model

An agent-based dynamic model uses a series of calculations to describe the interactions of independent objects. Drolet et al. used an HPV Agent-Based dynamic model to determine the added effectiveness of vaccinating multiple female cohorts with the HPV vaccine compared to routine vaccination at 12-13 years of age in Australia[19]. The model was calibrated to 678 pre-specified sexual behaviors to identify the model parameters[19] and comprised of 6 integrated components including sociodemographic characteristics, sexual behavior, HPV transmission, HPV related diseases, vaccination,

screening and treatments, and economics[19]. NNV was the secondary outcome and was calculated as:

$$\frac{The\ number\ of\ people\ vaccinated}{The\ number\ of\ events\ prevented}$$

An NNV of 9.9 for anogenital warts and 678 for cervical cancer was calculated for routine+catch up vaccination and 9.9 for anogenital warns and 677 for catch up vaccination[19], thus proving no added effectiveness of routine vaccination.

Doroshenko, who sought to investigate effects of outbreak response (ORI) targeting young adolescents for pertussis in Canada, also used the Agent-Based model to derive numbers needed to vaccinate that ranged from 49-221, from 130-519, and from 1031-4903; for all ages, the 10-14 age group, and for infants respectively[20]. He also calculated NNV by dividing the number of vaccinations delivered during ORI by the number of cases averted in the respective age group. Parameters included demographics, disease mechanism, disease propagation, vaccine coverage, and network characteristics and were derived from literature[20].

Advantages of this model are that it included age structure and quantified both vaccine-induced and natural disease derived waning immunity[20]. It is not, however, a useful standardized method, as it uses many parameters and assumptions that decrease its utility[20]. Also, the data needed for this model are not easily available (see Table 5) and the model is complex and difficult to understand.

Cohort Model

A cohort model is another widely used model used to calculate the NNV, as it is most sensitive to long-term effects of vaccination and allows for parameterization, like all

models. It was used by Brisson et al. in Canada to determine the NNV to prevent morbidity from both Herpes Zoster and HPV[10,11]. Parameters used in the model for HZ included vaccine efficacy, waning rate, HZ incidence rate, consultations, hospital rate, length of stay, case fatality, Quality Adjusted Life Years (QALY) and Post Herpetic Neuralgia (PHN.) An NNV of 11 for cases and 165 for QALY was calculated for HZ, proving the vaccine effective[11]. NNV was calculated as $^{N}/_{P}$, where N is the size of the vaccinated cohort and P is the predicted number of HZ cases prevented[21]. Using QALY was a significant strength of the model because the main benefit of vaccination is prevention of pain/suffering.

In the HPV study, the cohort model of HPV was developed using 209 parameter sets from Canadian data for infection, CIN, cervical cancer and warts. Model assumptions were that there was no cross protection between HPV types, transition rates between disease states were type and age-specific, co-infections with 2 HPV types could occur, women infected with 2 HPV types follow progression and regression rates of most aggressive type, and lifelong immunity could occur with HPV 16 and 18 but not with other HPV types[10]. Demographic, screening and treatment parameters were estimated from available data[10]. An NNV of 8 was calculated with an NNV of 14 when 3% waning immunity was accounted for. This proved effectiveness of the vaccine program.

The advantage of this model is that it calculates the NNV for the whole lifetime and provides information on both short term and long-term benefits. It is most sensitive to waning vaccine efficacy. It is not, however, useful as a standardized measure as it is challenging to get long-term data, as most randomized control trials are of short duration

and do not incorporate this information (see Table 5). It is also exceedingly complex and does not account for herd immunity.

MCMC simulation model

The MCMC simulation model is another model that was used to determine NNV. It is also complex and has the added disadvantage of not being able to include indirect effects of vaccination.

This model was used by Wattiaux in Australia to assess the potential impact of the hepatitis B immunization program[22] by running simulations through 100,000 scenarios. Variables in this model included age group, estimated population, estimated proportion of people susceptible to hepatitis B, estimated baseline number of infections/year and vaccine seroconversion rate[22]. An NNV of 149-181 was calculated when 25% of susceptible adults are vaccinated and 138-163 when 50% of susceptible adults were vaccinated. This was low enough to demonstrate usefulness of the vaccine program.

MCMC simulation models had also been used to demonstrate economic feasibility of vaccine programs. Ultsch et al. used a static MCMC simulation model, developed with 1 million individuals, to calculate an NNV of 10 and demonstrate economic feasibility of the herpes zoster vaccine in Germany[23].

This model was also developed by Annemans in Belgium to determine economic feasibility of the herpes zoster vaccine. It estimated the lifetime incidence of disease using input from Belgian data and literature sources, calculating an NNV of 12 [24].

The advantages of this approach are that it, like the agent-based model, has good internal validity and intensive parameterization and outputs the NNV. It is also an

effective combination of efficacy data from previous clinical trials. However, it is not a dynamic model, so herd immunity and mother and child-transmission cannot be factored in[22]. Also, there is absence of utility data considering the impact of health on quality of life.

Bayesian evidence synthesis approach

Finally, Bogaards et al. used a Bayesian evidence synthesis approach in the Netherlands in order to determine the reduction of burden of cancer if boys were vaccinated for HPV along with girls. Using this method, an NNV of 795 was calculated to prevent one case of cancer and prove the HPV vaccine advantageous for men[25]. Model parameters included risk of diagnosis, HPV attributable fraction, proportion who are HPV positive, and 10 years survival probability[25].

Advantages of this model are that it, again, has intensive parametrization and good internal validity, however it is also very complex and difficult to understand.

Advantages and Disadvantages of modeling-based NNV calculations

Despite the many strengths of modeling, we were not able to find a modeling method of calculating NNV that met the criteria to choose it as a standard measure. Modeling does have many strengths compared to other methods. Tuite et al. demonstrated the need to incorporate indirect effects of vaccination in the NNV formula[14] when she compared the static form of NNV calculation ($^{1}/_{ARR}$) to the dynamic form $^{Nc}/_{Nv}$, which was the ratio of vaccine doses(Nc) to cases prevented(Nv)[14] . It is also possible to estimate NNV to prevent one case in the patient's lifetime, whereas the NNV formula

$1/(incidence\ rate)(vaccine\ effectiveness)$ only detects the NNV for one year and therefore varies year by year depending on vaccine efficacy waning, coverage, vaccine effectiveness and background incidence. Modeling has many caveats, however, that do not support its use as a standardized method. Firstly, information on the long-term benefits/risks of vaccination is not necessarily available, as most randomized controlled trials are of short duration and do not measure vaccine waning (see Table 5). Because of the extensive parameters used and data needed, models are also exceedingly complex and difficult to understand by non-modelers. Finally, models are parameterized with the data from their specific country. Although this helps in extensive fitting, it would require local expertise to be able to run the model with data from other settings and is thus not generalizable.

NNT BASED METHODS TO CALCULATE NNV:

Number Needed to Treat Formula also derived a method that is most commonly used to calculate the NNV:

$$\frac{1}{Attributable\ Risk\ Reduction}$$

This formula is otherwise known as $1/(incidence\ rate)(vaccine\ effectiveness)$. The annual incidence of disease is usually represented by either incidence of hospital admission or population mortality, depending on whether the NNV is calculated per hospital admission or per death. This method was used by 17 studies and is one of the most common methods used to calculate NNV, as it is simple and easy to understand.

DeSerres et al. used this method to prove effectiveness of vaccinating healthcare workers to prevent patient deaths from influenza (NNV=32,688 in Canada and 6,000-32,000 in US)[30]. In this study, NNV was defined as 1/ARR, where ARR was the number of patient deaths attributable to hospital acquired influenza divided by the number of unvaccinated health care workers. Therefore, NNV could also be calculated as:

$$\frac{The\ number\ of\ unvaccinated\ health\ care\ workers}{The\ number\ of\ patient\ deaths\ preventable\ by\ vaccination}$$

This formula was also used by Steens et al. in a Norweigan study to determine the preventive potential of different vaccine strategies to prevent pneumococcal disease in the elderly[31]. NNV was calculated as

$$\frac{1}{Seasonal\ incidence\ in\ unvaccinated \times Vaccine\ Effectiveness}$$

Incunvac was defined as the seasonal incidence in the unvaccinated population and was calculated by dividing the predicted seasonal vaccine type count by the size of the unvaccinated population[31]. The NNV for the pneumococcal vaccine PCV13 (16,524) was larger than PCV23 (7149), illustrating that PCV23 would be effective.

Merk et al. also used this formula to determine the value of vaccination in Sweden[32]. It was calculated, in this case, as

$$\frac{1}{VE \times ({}^{cases}/_{n})}$$

In this formula, VE was the vaccine effectiveness, 'cases' was the total number of influenza hospitalizations in pregnant women per season, and 'n' was the number of unvaccinated pregnant women[32]. The VE range was very wide in this study, and the NNV

was calculated for both sides of the confidence limits. It was determined that over 1900 women needed to be vaccinated, which was higher than in USA, Canada and UK.

In a study in US by Lewis et al., to determine that the influenza vaccination program could reduce influenza-attributable medical visits in children, ARR was calculated as the published rates of influenza attributable illness*vaccine efficacy and was used to compute an NNV of 4255-6927 for children 24-59 months and 1031-3050 if 6-23 months[4].

Kelly et al. used the NNV to determine that 1852 children in Australia would have to be vaccinated to prevent one hospitalization due to any strain of influenza[33]. In this case, NNV was calculated as $^{1}/_{ARR}$, where ARR was the absolute risk in unexposed/unvaccinated*relative risk reduction[33]. The formula for NNV was, therefore:

$$\frac{1}{Absolute\ risk\ in\ unexposed \times relative\ risk\ reduction}$$

The relative risk reduction was the vaccine effectiveness. The hospitalization rate in the unvaccinated was the absolute risk in the unexposed/unvaccinated and was calculated as the number of unvaccinated children in the hospital/estimated number of unvaccinated children in the population[34].

Saglioca also used a NNV of 18 calculated by 1/ARR to demonstrate the effectiveness of hepatitis A vaccine in Italy in preventing secondary infection[35].

This method was also used in a study by Vila Corcoles et al., where an NNV of 239 was calculated to prove that the influenza vaccination program affected mortality in a Spanish community during winter months[36].

One of the issues with this using this method to calculate NNV was that ARR could be calculated in many different ways. For example, in a study by Lopez-Gigoso et

al., NNV was calculated to determine the effectiveness of a vaccine that prevents travelers' diarrhea, and was calculated as 1/ARR. ARR, however, was expressed as a proportion per 100, and VE was calculated as 1-RR, determined from a fitted regression model[37].

Cost-Effectiveness of Cocooning Vaccine Programs:

NNV had also been calculated as $^{1}/_{ARR}$ to determine the cost effectiveness of cocooning. In a study in Spain by Fernandez-Cano et al., $^{1}/_{ARR}$ was used to determine the NNV for pregnant women, and the NNV for cocooning was determined by $^{2}/_{ARR}$ as there are two parents[38]. The absolute reduction in hospitalization risk for infants was

$$vaccine\ efficacy \times proportion\ of\ infants\ with\ maternal\ antibodies \times hospitalization\ risk\ + \\ vaccine\ efficacy \times (1 - proportion\ of\ infants\ with\ maternal\ antibodies)$$

NNV was calculated as 4752 to prevent a hospitalization of pertussis and 900,000 to prevent a death with cocooning, deeming that more effective.[38]

Other studies that determined the cost effectiveness of the cocoon program were by Skowronski et al. in Canada and Meregaglia et al. in Italy, where the cocoon program was proven economically not feasible by using the method $^{2}/_{Parent\ attributable\ infant\ risk \times parent\ vaccine\ effectiveness}$ to calculate an NNV of 10,000[7,17].

With this method, it was possible to see the order of magnitude of resources and involvement to achieve program goals. It was, however, predicated on surveillance data, and therefore could not be generalized. Also, a potential disadvantage is limiting the effects of cocooning only to parents and not including other family members.

Cost-Effectiveness of Vaccine Programs:

$1/_{ARR}$ was also used to determine cost-effectiveness of vaccine programs. In a study by Dang et al. in Canada, the inverse of infant age-specific incidence*expected vaccine efficacy was used to calculate an NNV of 33784-38610 and demonstrate that prospective funding of meningococcal vaccines was not feasible[9]. The inverse of age-specific incidence of the infant was calculated and multiplied by the expected vaccine efficacy, using the observed annualized age-specific incidence among infants and a vaccine efficacy ranging from 70 to 80%[9]. The vaccine efficacy range was chosen to give a conservative estimate of NNV, as there are currently no efficacy studies published on novel meningococcal B vaccines.

Cost effectiveness of the influenza vaccine program was also proven in the US by Patel et al., who used NNV to calculate a cost of $37,621 per life year saved over the study period by calculating NNV as:

$$\frac{1}{population\ all-cause\ mortality\ rate \times vaccine\ efficacy\ against\ all-cause\ mortality}$$

Kelly et al. used the same method in Australia with information on annual disease attack rate, VE, annual incidence and population mortality to determine to determine that the costs for influenza ($74,801/death/year) and pneumococcal vaccine programs ($49,972/death/year) were similar [5].

Hillemanns et al. used $1/_{ARR}$ to derive an NNV of 120, which supported the German national HPV program as cost effective[6].

Finally, DeSerres in US calculated an NNV of 314,000-2.7 million using the same formula to determine that post exposure prophylaxis for rabies was not economically feasible[8].

Advantages/Disadvantages of $1/_{ARR}$:

This method meets many of the criteria described earlier. It combines the burden of disease and vaccine effectiveness into a single, clinically relevant measure[4]. It is very intuitive and simple to understand and is a clinically relevant measure that can be used to estimate potential reduction in infection, given the current vaccine recommendations[4]. It is also directly related to the proportion of the population exposed and provides insight into the benefit-to-risk ratio of a vaccine[8].

Information needed to calculate $1/_{ARR}$ is also easily available and measured in most randomized controlled trials (see Table 5). This information includes annual disease attack rate, published vaccine effectiveness estimates, annual incidence of admission, population mortality rate, rates of disease-attributable illness, number of human cases due to exposure without intervention and % exposed per year in person-years. For cocooning programs, additional information is needed on the parent's vaccine effectiveness and parent attributable infant risk, where parent-attributable infant risk was calculated as infant risk*proportion of infants infected by parents[7]. These data are highly predicted on surveillance of administrative data, however, which could affect the validity and generalizability of the findings.

The reason that this may not be an ideal method is that data used in this formula are specific to date and time, however, measures are only useful when comparing vaccine

programs targeted at the same population, as consequences of events due to disease are not always comparable. This study by Merk demonstrated the need for a standardized NNV, as it was proven difficult to compare NNV between countries when different methods were used. It also does not take into account indirect effects of vaccination or long term effects of vaccination, and therefore produces biased estimates. Also, number needed to treat is effective because the direct costs and benefits are clear, as they apply to a shorter time period and occur in close temporal relationship to exposure[13]. When the NNV is derived from the number needed to treat, however, it cannot show as direct a relationship, as vaccinations are preventive and the exact time or extent of exposure is generally not known[13]. When diseases are approaching elimination, the NNV becomes large and is misleading, as the reason that the NNV becomes large is that the incidence is reduced[13]. Finally, in the case of influenza, vaccine effectiveness, incidence and severity of disease changes every year and so NNV varies every year, also, data from multiple seasons may need to be combined[4].

An analysis by McLaughlin offered a solution to some of these limitations. In this analysis, two methodologies were compared: (i) Using the one-year absolute rate differences as performed by the Centers for Disease Control and Prevention and (ii) Using absolute risk reduction over 5 years[1]. It was determined that the standard method that has been used to calculate NNV from Number Needed to Treat (NNT) was using annual or seasonal incidence rates instead of cumulative incidence to obtain the attributable risk reduction[1]. Because of this, only short-term effects of vaccination were being included in this calculation. When cumulative incidence was used instead, however, this incorporated long-term effects into the calculation and took into account

factors such as waning immunity. When both methods were compared in this analysis, it was determined that the NNV that used cumulative incidence was almost one-third the NNV that used annual incidence[1]. This is a significant difference that can have a dramatic impact on the NNV. This method has not been used significantly in literature, however, and requires more testing to be considered as a standardized method.

1/ARR/VACCINE PERIOD LENGTH

There are, however, other methods that take into account long-term effects of vaccination. To determine whether individuals with asthma should be vaccinated with PCV13 or PCV23 to protect against Invasive Pneumococcal Disease (IPD), Okapuu calculated NNV as:

$$\frac{1}{\frac{ARR}{estimated\ length\ of\ vaccine\ protection}}$$

The absolute risk reduction was the difference in the disease incidence between the unvaccinated and vaccinated. The NNV was thus, $1/_{VP\ length \times (1/incidence\ unvaccinated - incidence\ vaccinated)}$ and was calculated as 1097-1239 in health individuals, 704 to 820 in low risk individuals, and 386-449 in high-risk individuals[39].

Wilder Smith et al. also used a similar method to determine that NNV and vaccine preventable disease incidence (VPDI) are more useful to inform decisions on regulatory approval and vaccine policymaking than a measure like vaccine efficacy, which does not capture the full benefit of vaccination. VPDI measures the difference in the incidence of any outcome between a vaccinated and unvaccinated population. NNV is

the overall number of cases prevented for a given number of persons vaccinated, and thus incorporates the duration of immunity. Therefore, if the VPDI, which is calculated as $outcome\ incidence\ in\ unvaccinated \times vaccine\ efficacy$, is reported as cases per 100,000 vaccinated persons, the NNV would be $100{,}000/VPDI/length\ of\ study$[12]. This took into account vaccine immunity duration. Gessner et al. also used the same formula to determine the public health importance of the dengue vaccine by calculating an NNV of 18 to prevent virologically confirmed dengue in the Asian Pacific trial and 28 in Latin America, with an NNV of 75 and 201 respectively to prevent hospitalization[40].

This method meets the most criteria of a standardized calculation to detect NNV. It includes the vaccine period length of study, and therefore the value is not affected by length of vaccine period. There is also more utility of this approach when calculated for clinical outcomes, as the immune duration is taken into account and so waning effectiveness will not affect the VPDI and NNV. It is also a simple approach and is easily understandable by the population. The disadvantages are that serotype replacement and herd immunity are not factored in. Also, the NNV calculation can only be done if the number of persons vaccinated by the intervention and control populations is available. There may be problems obtaining the immune duration, distribution of disease burden within countries and vaccine schedule requirements.

OTHER METHODS TO CALCULATE NNV

Other methods had also been used to calculate the NNV to determine the effectiveness or cost effectiveness of a vaccine program. As these methods are not widely

used, they are not the best choices for a standardized method to calculate NNV but will be mentioned briefly for completion.

Sorup et al. calculated NNV in Denmark by estimating risks for first admission in children who received Measles Mumps Rubella vaccine (MMR) through an adjusted Cox analysis and calculated an NNV of 93 to vaccinate with MMR to prevent 1 hospitalization based off of the risk difference[41]. This NNV was calculated to determine whether MMR was associated with lower rates of hospital admissions for infectious diseases in Denmark. Another method used in this paper was estimating risk difference using $(1 - exp^{-IR}) - \left(1 - exp^{-IR \times adjusted\ IR}\right)$.

This method was also used by Voordouw et al. in Netherlands to determine that annual influenza vaccination was associated with a reduction in all-cause mortality by calculating an NNV of 302 to prevent one death[18]. Strengths of this study were that it was able to assess the annual and epidemic effectiveness of annual influenza vaccinations as well as effect of individual revaccinations[18]. It was also able to adjust for confounding by chronic respiratory tract disease, cardiovascular diseases and other chronic illnesses[18]. The limitation to this method is that it is not as simple as using NNT, as SAS was used for analysis, using the procedure Proc Phreg[18]. Factors that went into calculation and interpretation included vaccination coverage from 1996 to 1997, information on the influenza epidemics, and vaccine effectiveness information[18].

Mooney et al. used an adjusted vaccine effectiveness adjusted for age and sex to determine that an NNV of 5206 proved that the vaccine program for IPD was effective in Scotland[42].

Lindsay et al. used an adjusted risk difference according to stage of pregnancy and translated this to NNV (when VE was incorporated) to determine whether influenza activity in the community was associated with increased risk of influenza like illness during pregnancy[43]. An NNV of 20-43 was calculated to prevent one influenza-like illness episode.

In another study by Crowcroft et al., the formula $R = a(1-k)(n-1)$ was used to calculate the NNV for hepatitis A vaccination programs[44]. In this formula, R was the average number of secondary cases in each household after a case, n was the size of the household, a was the AR in susceptible contacts and k is the protective efficacy of the intervention[44]. The difference in the number of secondary cases between vaccines could be calculated for different vaccine effectiveness values, comparing the vaccine and HNIG. The inverse of this number would be the households needed to treat with the vaccine to prevent one secondary case of hepatitis A[44]. This was done to measure the number of households that need to be vaccinated in UK with hepatitis A (8-26) to prevent one secondary case of hepatitis A.

To measure cost effectiveness, Trunz et al. used the formula $^{1}/_{5\lambda\rho men\varepsilon men^{3}}$. This was the formula used to obtain the expected number of cases of tuberculosis meningitis after infection was acquired by children for 5 years of peak risk after birth. B was the number of children born in 2002, λ was the annual risk of infection, and ρ_{men} was the proportion of infections that leads to meningitis in unvaccinated children between 0-4 years[3]. Data needed to calculate this method included annual risk of infection, per capita contact rate for each smear positive case, proportion vaccinated, and vaccine effectiveness[3]. Limitations of this method are that it does not account of indirect effects

of vaccination. Also, it was assumed that vaccine coverage and risk of infection are uniformly distributed, when this may not be true and may lead to overestimation of vaccine effect if vaccine coverage is higher in communities where risk of tuberculosis is low[3]. Finally, it is difficult to derive annual risk of infection, as the contact rate was estimated on the basis of approaches used in only 11 countries, and has very wide confidence intervals[3].

Rahman also did an analysis to compare the cost and number of immunizations needed to prevent a single case of Tb by the universal BCG vaccine program versus no vaccination in Japanese infants[2]. The formula that was used was:

$$\frac{Total\ number\ of\ immunizations\ (PV \times N \times 100{,}00)}{Total\ number\ of\ TB\ cases\ averted\ (Ptb + Pextb + Pttb)}$$

In this formula, PV was the proportion of vaccinated infants, N was the number of population, P_{tb} was the number of cases prevented by the vaccination program, P_{extb} was the extra TB meningitis cases due to differing efficacy of vaccine against TB, and P_{ttb} was the number of cases averted by breaking the transmission chain, which would be equal to (P_{tb} +P_{extb})+3*0.0065.

INFORMATION AVAILABLE TO CALCULATE NNV:

Through review of 53 randomized control trials, it was assessed how many randomized control trials collected each of the following parameters[45-105].

Table 4:

	Rotavirus	**Pneumococcal**	**Influenza**

		Disease	
Demographics			
Age	19	15	19
Gender	19	15	19
Race	6	7	9
Mother Education		1	2
Family Income	2		1
# People Household	1	2	2
Smoking	0	4	3
Comorbidities	1	7	4
Other treatment	0	0	2
Follow Up Time	9	6	2
OPV dose	5	0	1
Physical characteristics			
Weight at enroll	5	1	1
Birth Weight	2	0	1
Length/Height	5	0	1
Weight-for-age	0	0	1
Height-for-age	0	0	1
Vaccinated			
Vaccine Efficacy	19	18	19
Number vaccinated	19	18	19
Number	19	18	19

unvaccinated			
Cases detected			
Cases detected	12	10	10
Hospitalization	11	10	9
Antibody			
IgA levels	13	-	-
Seroconversion	14	11	12
Antibody titers	13	11	12
Adverse Effects			
AE/SAE	17	13	14
Other			
Rotavirus shedding	5		
Herd Immunity	1	2	
Length of Study	19	15	19

From this review, it is clear that the information needed for calculating NNV from the formula 1/(vaccine effectiveness)(incidence of disease) is available. There is also information present on the length of the study. Information that is not collected usually pertains to the long-term effects of vaccination. For example, parameters such as herd immunity, mother to child transmission and duration of protection by the vaccine are usually not collected by these studies unless a separate post-hoc analysis is done.

DISCUSSION:

Table 6 summarizes which of the methods is most useful as a standardized method.

Table 5:

	Simple	Information available	Accounts for indirect methods	Accounts for long-term effects of vaccination
Agent-Based Model	-	-	+	+
Cohort Model	-	-	-	+
MCMC Model	-	-	+/-	+
Bayesian Synthesis Model	-	-	+	+
1/ARR	+	+	-	-
1/ARR/Study Length	+	+	-	+

We determined that the formula $1 \div {ARR}/{Length\ of\ Study}$ meets the most criteria to calculate the NNV as it is simple, intuitive, accounts for long term effects of vaccination, and contains information that is easily available.

Modeling based results, though they may produce the most accurate result and accounts for indirect effects of vaccination, are not widely understood by decision-makers[14]. These estimates require information that is easily available, as they are extensively parameterized and need specific information on long term effects of vaccination, most of which are not collected in randomized control trials. Also, though modeling-based estimates can account for indirect effects of vaccination, some of these effects can only be accounted for in certain types of models. For example, only dynamic models can include information on herd immunity.

1/ARR (where ARR=vaccine effectiveness*incidence rate) meets more of the characteristics of an ideal standardized method to calculate NNV. It is simple, intuitive, and contains information that is easily available and generally collected in randomized control trials. It is also widely used in literature as a standardized method to calculate the NNV and has thus been proven effective many times. The problem with this method is that it does not take into account the long-term effects of vaccination. As the annual incidence rate is used in the calculation of ARR, this calculation of NNV does not account for the length of the study period or changes in vaccine efficacy over a period of time[1]. As vaccination's main benefit lies in its long-term protection, this is not a viable method to calculate the NNV.

$1 \div {ARR}/{Length\ of\ Study}$, or $100{,}000 \div {VPDI}/{Length\ of\ Study}$ meets the most criteria to calculate the NNV. In this calculation, NNV is not a rate but the overall number of cases prevented for a given number of persons vaccinated. This method is simple, intuitive, and contains information that is easily collected in randomized control trials. It has been used in three studies that have demonstrated the public health

importance of vaccines[12,39,40]. It also takes into account the long-term effects of vaccination. The primary flaw is that it does not account for herd immunity, however, conventionally herd immunity is not included in calculations of NNV. Though herd immunity contributes significantly to indirect effects of vaccination that do provide substantial benefit, it is again, population specific and depends on contextual factors such as vaccine coverage[106]. Therefore, this method still appears to be the most effective method to calculate the NNV.

Limitations of this review are that even if the same methods are used between countries, there will still be differences between countries due to different data acquisition methods and differing data quality. Another limitation is that the NNV, even if the same method is used, is pathogen-specific. For example, influenza data usually grossly underreports or over-reports, which can change the NNV estimate considerably. Therefore, regardless of the method that are used, it is necessary to advocate proper surveillance of data regarding infectious disease, especially when it comes to developing international standards for data acquisition. Without this, full standardization of methods will not be possible.

CONCLUSION

For data to be compared effectively and used comprehensively to lower global burden of infectious disease, methods of calculation of statistical measures such as the NNV need to be standardized. Through this review, the advantages and disadvantages for each method of calculation of NNV are examined in detail and can be used for development of a standard method of NNV calculation.

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APPENDIX 1

Table 1- Differences in Interpretation of NNV

Research Question	Method	NNV	Does NNV support vaccine related policy-making?
Can influenza vaccination reduce influenza-attributable medical visits?[4]	1/Attributable Risk Reduction	4255-6927 (24-59 months) 1031-3050 (6-23 months)	Yes
Is the vaccine for IPD effective ?[5]	1/Attributable Risk Reduction	5206	Yes
Is the HPV vaccine cost effective?[6]	1/Attributable Risk Reduction	120	Yes
Is the cocoon program cost effective?[7]	1/Attributable Risk Reduction	10,000	No
Is post exposure prophylaxis for rabies feasible?[8]	1/Attributable Risk Reduction	314,000-2.7 million	No
Does the funding of meningococcal vaccines seem feasible?[9]	1/Attributable Risk Reduction	33,784-38,610	No
What is the NNV to	Cohort Model	324	Yes

prevent morbidity due to HPV?[10]			
What is NNV to prevent morbidity due to Herpes Zoster (HZ)?[11]	Cohort Model	11	Yes
Is TB vaccine cost effective?[3]	Other	9,000	Yes
Is the current BCG vaccine cost effective?[2]	Other	2125-10,399	No

Table 2- Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Should interpret number needed to vaccinate	The full text was not available
Should either calculate NNV as a primary measure or analyze NNV	It was a meta-analysis that does not detail the methods
Should detail NNV calculation in methods if calculated	The study was done for non-humans
Should be in English	
Should include NNV in the title or abstract	

Figure 1- Method for Literature Review

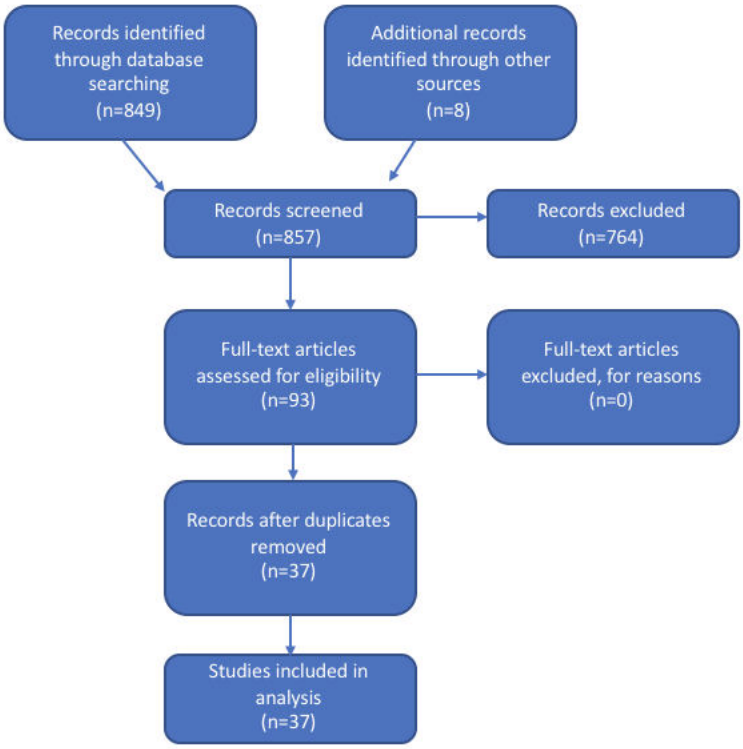

Table 3- Characteristics of Study Results

CHARACTERISTICS OF STUDY RESULTS (N=37)	
Purpose of calculating NNV	
Assessed effectiveness of a vaccine program	22
Assessed public health importance of a vaccine	3
Assessed cost effectiveness of a vaccine program	12
Method of NNV calculation	

Method based on NNT	17
Modeling	9
Other	8
Analysis of NNV	3

Table 4- Information Available in Randomized Control Trials

	Rotavirus	**Pneumococcal Disease**	**Influenza**
Demographics			
Age	19	15	19
Gender	19	15	19
Race	6	7	9
Mother Education		1	2
Family Income	2		1
# People Household	1	2	2
Smoking	0	4	3
Comorbidities	1	7	4
Other treatment	0	0	2
Follow Up Time	9	6	2
OPV dose	5	0	1
Physical characteristics			
Weight at enroll	5	1	1

Birth Weight	2	0	1
Length/Height	5	0	1
Weight-for-age	0	0	1
Height-for-age	0	0	1
Vaccinated			
Vaccine Efficacy	19	18	19
Number vaccinated	19	18	19
Number unvaccinated	19	18	19
Cases detected			
Cases detected	12	10	10
Hospitalization	11	10	9
Antibody			
IgA levels	13	-	-
Seroconversion	14	11	12
Antibody titers	13	11	12
Adverse Effects			
AE/SAE	17	13	14
Other			
Rotavirus shedding	5		
Herd Immunity	1	2	
Length of Study	19	15	19

Table 5- A Comparison of Methods to Calculate NNV

	Simple	Information available	Accounts for indirect methods	Accounts for long-term effects of vaccination
Agent-Based Model	-	-	+	+
Cohort Model	-	-	-	+
MCMC Model	-	-	+/-	+
Bayesian Synthesis Model	-	-	+	+
1/ARR	+	+	-	-
1/ARR/Study Length	+	+	-	+