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Review

How and why researchers use the number needed to vaccinate to inform decision making—A systematic review

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ABSTRACT

Background*:* The number needed to vaccinate (NNV) is a measure that has been widely used in the scientific literature to draw conclusions about the usefulness and cost-effectiveness of various immunization programmes. The main objective of this review is to examine how and why the NNV has been used and reported in the published literature.
Methods*:* Electronic databases were searched and records were screened against the eligibility criteria by two independent authors. We included papers that reported and interpreted NNV.
Results*:* We identified 27 studies, the designs including observational studies, economic analyses, systematic reviews, and commentaries. The NNV has been used in the literature to describe three main themes: potential benefits of vaccination programmes, cost-effectiveness, and economic analyses, and modelling studies to compare different vaccination strategies.
Conclusions*:* NNV has been used in a wide variety of ways in the literature, yet there are no defined thresholds for what is a favourable NNV. Furthermore, the generalizability of the NNV is usually limited. Further work is required to determine the most appropriate use of this measure.

1. Introduction

Vaccines have saved more lives than any other health intervention in the last century. The World Health Organization estimates that more than two million deaths annually are prevented due to immunization programmes worldwide [1]. Despite this measurable impact, the benefits of immunization are sometimes taken for granted, which can pose a significant challenge [2,3]. Sustaining the priority of vaccine-preventable diseases in the eyes of the public and policy makers is more difficult when these diseases are well-controlled because they are out of sight and therefore out of mind. The benefits of immunization need to be promoted using simple and intuitive measures that enable fair comparison with other competing priorities.

The number needed to vaccinate (NNV) is used as a simple summary calculation to evaluate the possible benefits of immunization programmes in preventing and controlling communicable diseases. It is defined as the number of persons needed to vaccinate in order to prevent one outcome, and it combines both vaccine effectiveness and incidence of disease [4]. Generally, the NNV is calculated as NNV = 1/(annual incidence of event in the unvaccinated × vaccine effectiveness (VE)). This is equivalent to the reciprocal of the annual absolute risk reduction, since the VE measures the relative risk reduction. [4]

In recent years there have been an increasing number of analyses that use NNV to evaluate the usefulness and cost-effectiveness of several vaccines. Although NNV is an intuitive measure of the benefit of a given vaccine, there remains no agreed threshold for interpreting this number, and questions have been raised as to whether it is an appropriate measure [31]. This systematic review aims to explore how and why NNV is used in the scientific literature in order to draw conclusions about the appropriate use of NNV for public health decision making.

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2. Methods

We searched the online databases MEDLINE, EMBASE, and CINAHL in February 2013 for all primary research studies that have reported, calculated, and interpreted NNV. We included all review articles, commentaries, and published letters that reported and interpreted NNV. Studies that did not interpret NNV were excluded. Search strategy was restricted to English-language publication on human subjects. Eligibility criteria were applied to examine all the records at the title, abstract, and full text stages. This was conducted systemically by two reviewers (AH and VD) using Microsoft® Office Excel® 2007 version 12 (Microsoft Corporation, Richmond, USA). Discrepancies between the two reviewers were resolved through consensus. If the title or abstract of a given study was not enough to determine inclusion or exclusion from our study, the full texts were assessed against the same criteria. In addition, the references of all articles were reviewed for other potentially eligible studies. The search strategy used the following terms: "number-needed-to-vaccinate" or "NNV" or "prevent case or illness or death or outcome or event or disease or hospitalisation or hospitalization" and "vaccination or immunisation or immunization". Data extracted from the eligible studies comprised of study objectives, study design, NNV definition, vaccine type, disease outcome, population characteristics, parameters used in calculating NNV, vaccine effectiveness, and interpretation.

Table 1
Number of studies by study design and vaccine type.

Characteristics	Number of studies
Study design	
Observational studies	9
Economic evaluation	7
Systematic reviews +/− Meta-analysis	6
Commentary	3
Modelling	2
Vaccine type	
Influenza	8
Tuberculosis	4
Herpes Zoster (HZ)	3
Human Papilloma Virus (HPV)	3
Pertussis	3
Hepatitis A	2
Pneumococcal	2
Meningococcal B (MenB)	1
Respiratory Syncytial Virus (RSV)	1
Rabies	1
Outcome	
Case	20
Death	7
Hospitalization	6
Outpatient visit	1
Quality-adjusted life year (QALY)	1
Disability-adjusted life year (DALY)	1
Life-years lost	1

3. Results

3.1. Study selection and characteristics

The initial search resulted in 432 entries, of which 11 were duplicates; 393 were excluded on the basis of our screening criteria at the title and abstract stage. At the full-text screening stage, five records were excluded for not meeting the inclusion criteria. Reference and citation tracking identified an additional four eligible papers, providing a total of 27 papers for review. Fig. 1 illustrates a flow diagram of the study selection process.

The disease outcomes reported were influenza in eight studies [4–11], tuberculosis in four studies [12–15], as well as three studies each of herpes zoster (HZ) [16–18], human papilloma virus (HPV) [19–21], and pertussis [22–24]. Two studies each focused on Hepatitis A [25,26] and pneumococcal disease [4,27]. Other disease outcomes included serogroup B meningococcal disease [28], respiratory syncytial virus (RSV) [29], and rabies [30]. Outcomes for which NNVs were measured included being a case of a specific disease, death, hospitalization, outpatient visit, quality-adjusted life year (QALY), disability-adjusted life year (DALY), and life-years lost. One third of the included studies ($n = 9$) used data from observational studies, which were primarily cohort studies [8–10,12,17,23,27,28,30]. In addition, seven studies were cost-effectiveness and economic analyses [4,5,13,15,16,21,22], six studies were systematic reviews [6,7,11,14,26,29]; three were commentaries [18,20,25], and two studies utilized mathematical modelling [19,24]. Study characteristics of the included studies are summarized in Table 1.

3.2. How is NNV being used in the literature?

3.2.1. Potential health-related benefits of vaccination programmes

Fourteen studies (52%) used NNV as a measure of potential benefits of vaccination programmes.

Of these, five articles in the literature utilized NNV to measure the potential benefit of influenza vaccination using different health outcomes. Kelly and colleagues [10] quantified the benefits of an influenza vaccination programme by calculating the number of persons required to be vaccinated to avoid one hospital admission due to influenza. They reported that 1852 children would have to be vaccinated to avoid one hospitalization due to any strain of circulating influenza in 2009. Lewis and colleagues also quantified the numbers of children who needed to be vaccinated to prevent one hospitalization and outpatient visit [7]. This was found to range from 1031 to 3050 for children 6–23 months of age and from 4255 to 6897 for children 24–59 months of age. They estimated that 12–42 children 6–59 months of age need to be vaccinated to prevent one outpatient visit, and that vaccination was therefore an important means of reducing influenza associated outpatient visits in this age group. Similarly, two other studies used NNV to measure the benefits of influenza vaccination in preventing influenza and cases of influenza-like illness in pregnancy and postpartum women, and HIV-infected individuals, respectively [8,11]. Voordouw and colleagues investigated the benefit of influenza vaccination for preventing all-cause mortality. The authors stated that in order to prevent one death due to influenza, it is required to vaccinate 302 individuals or one for every 195 repeated vaccinations at a vaccination coverage up to 74%. They concluded that the annual influenza immunization of the elderly population has the potential to reduce all-cause mortality [9].

Two studies used NNV to evaluate the potential benefits against HZ. Skootsky described the NNV as an alternate measure of efficacy against HZ [18]. It was reported that one case of HZ was avoided for every 175 adults over 60 years of age who were vaccinated, and one prevented for every 231 adults 70 years of age or older. A similar analysis for patients 70 years and older showed that 231 people needed to be vaccinated to prevent one episode of HZ. Skootsky concluded that these numbers are greater than what many physicians and most patients might expect (although what would be expected was not defined precisely) and therefore a less attractive HZ vaccination programme. In another HZ study, Brisson [17] estimated the NNV for various HZ related health outcomes for patients who are 65 years. Brisson estimated that the NNV to prevent a case of HZ is 11, to prevent a case of post herpetic neuralgia (PHN) is 43, to prevent an HZ death is 23,319, to prevent a life-year lost is 3762, and to prevent a lost QALY is 165. The study stated that,

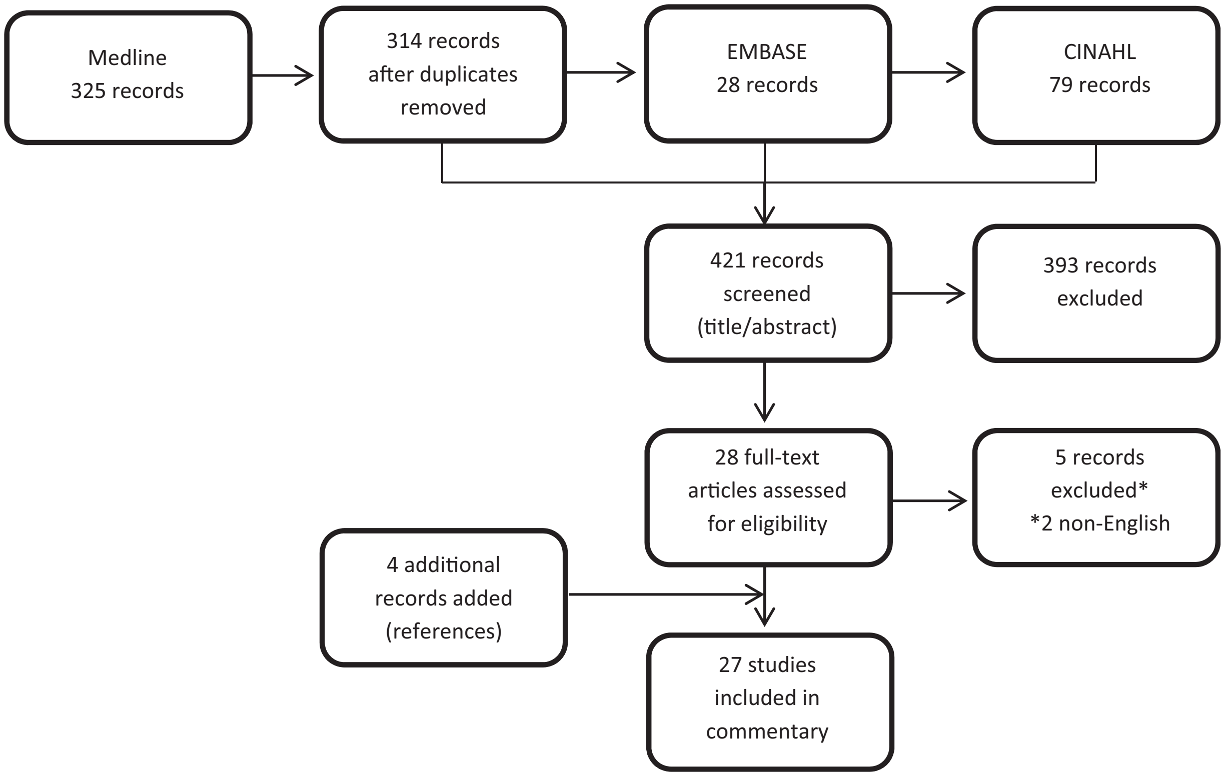

Fig. 1. Flowchart showing literature search strategy. Medline, EMBASE and CINAHL databases were searched for appropriate literature. After removal of duplicates, 421 records were screened. Of these, 27 met the criteria for inclusion in this review.

since the NNV to prevent a QALY lost is significantly less than the NNV to prevent a life-year lost, the main benefit of HZ vaccination is the prevention of pain and suffering, rather than mortality. The study concluded that the NNV can be used intuitively by clinicians to inform their patients of the potential benefits of HZ vaccination and by public health officials as a measure of the preventable burden of disease through vaccination [17].

Several other studies were conducted to evaluate the benefits of vaccination against other diseases. Kelly et al. reported a NNV of 646 to prevent one case of tuberculosis in 1986, and 551 in 1991. They concluded that this evidence supports a policy of continued neonatal Bacillus Calmette-Guérin (BCG) vaccination in the population of the Republic of Ireland [12]. One study from the UK reported that 5206 persons are required to be vaccinated to prevent one invasive pneumococcal disease. In this study, NNV was communicated as an alternative way to demonstrate the overall effectiveness of the vaccination programme [27]. An editorial by Sawaya and Smith calculated the NNV for a clinical trial (FUTURE II) that measured HPV vaccine efficacy. It was found that 129 persons needed to be vaccinated against HPV in order to prevent one case of cervical intraepithelial neoplasia [20].

Dang et al. calculated the NNV for serogroup B meningococcal disease, and estimated that between 33,784 and 38,610 infants would need to be vaccinated in order to prevent one case of serogroup B invasive meningococcal disease. The number would be even higher to between 123,751 and 141,429 if cases in infants under six months of age were assumed to not be vaccine preventable. The authors concluded that this was very high and made the vaccine unlikely to be an attractive policy option. Since there are currently no licensed meningococcal B vaccines in Canada, the calculations in this study were mainly based on several assumptions including hypothetical vaccine efficacy and vaccine uptake, and an assumption that there was no herd immunity, resulting in a conservative NNV estimate [28].

Crowcroft calculated the number of households that need to be vaccinated with hepatitis A vaccine instead of human normal immunoglobulin (HNIG) to prevent one secondary case of hepatitis A. The study found that 8–26 persons would need to be vaccinated to prevent an additional secondary case. Such significantly worse outcomes were unlikely to be observable by public health professionals in the context of very low disease incidence [25]. In this study, NNV was used to evaluate the ability of the public health system to distinguish between the effectiveness of different interventions.

In addition to primary studies utilizing the NNV to describe the potential benefits of vaccination programmes, two systematic reviews and meta-analyses were identified. Jefferson and colleagues conducted a systematic review and meta-analysis to measure influenza vaccine effectiveness and efficacy in healthy children [6]. They used NNV to compare prevention of laboratory confirmed influenza by live attenuated vaccine with that of inactivated vaccines and reported an NNV of seven for live attenuated and an NNV of 28 for inactivated vaccine. Simoes and colleagues [29] conducted a systematic review and meta-analysis of clinical trials of experimental RSV vaccines for individuals 12 months and older to explore whether RSV vaccines are efficacious in preventing RSV lower respiratory tract infection, but conclusions were limited by heterogeneity between studies.

3.2.2. *Cost-effectiveness analysis*

Eleven studies (41%), including seven economic analyses [4,5,13,15,16,21,22], two observational studies [23,30] and two systematic reviews [14,26] interpreted NNV in the context of a cost-effectiveness analysis of vaccination programmes.

Three studies identified in the literature measured the cost effectiveness of tuberculosis vaccination programmes. Trunz and colleagues conducted a systematic review to assess the cost-effectiveness of childhood immunization programmes to prevent tuberculosis meningitis and severe tuberculosis worldwide [14]. They estimated that around 150,000 children should be vaccinated to prevent one case of tuberculosis. The authors commented that immunization programmes against tuberculosis are cost-effective to prevent and control childhood tuberculosis particularly in high-incidence countries. In another study in the Netherlands, it was estimated that around 9000 would need to be vaccinated to prevent one severe tuberculosis infection. They presented their results in terms of cost/DALY to be spent on vaccination; NNV for the target group corresponded to €4500/DALY, which lies below the threshold considered "reasonable" for public health intervention, thus it was concluded that the immunization programme in Netherlands is cost-effective [13]. On the other hand, Rahman et al. conducted a cost-effectiveness analysis of the Japanese BCG vaccination programme. This study estimated that between 2125 and 10,399 immunizations at the cost of US $35,950–$175,862 would be required to prevent one case of tuberculosis. They concluded that universal BCG vaccination programme is not cost-effective approach since the immunization cost was higher than the cost required to treat one patient with tuberculosis infection [15].

Two studies have assessed cost-effectiveness using NNV of the 'cocooning' immunization strategy, whereby parents and other close contacts of an infant are vaccinated with tetanus, diphtheria and acellular pertussis vaccine, to protect newborn infants from pertussis infection. Meregaglia et al. estimated that at least 5000 parents needed to be vaccinated, at a total cost of more than €100,000 to prevent one pertussis-related hospitalization. They concluded that the parental cocoon strategy is not a cost-effective approach in preventing pertussis in this age group [22]. Likewise, Skowronski and colleagues reported that the NNV for the cocooning immunization strategy against pertussis was around one million to prevent one infant death and approximately 10,000 for hospitalization. Like Meregaglia and colleagues, they described the cocooning immunization programme as a non-cost effective strategy [23]. In another study, similar in considering a targeted strategy for a high risk group, Rowe et al. evaluated the use of routine hepatitis A vaccination in hepatitis C infected persons, concluding that it is costly and its incorporation into clinical practice guidelines is not recommended [26].

Kelly and colleagues conducted a cost-effectiveness analysis to compare the potential benefits of the influenza and pneumococcal vaccination programmes in the elderly population. Although the cost to prevent a case of influenza infection per year is less than the cost to prevent a case of invasive pneumococcal disease ($598 vs. $11,494), the cost for the prevention of one hospitalization due to influenza and pneumococcal disease is similar in both programmes ($10,787 and $11,494 respectively). The vaccine cost to prevent one death per year is less for the pneumococcal vaccine programme ($49,972 vs. $74,801). They inferred that since the vaccine costs associated with hospitalization or death due to invasive pneumococcal disease were similar or cheaper than for influenza, it is likely that a pneumococcal vaccine programme would also be likely to be cost effective in this age group [4].

Three other studies showed cost-effectiveness of influenza, human papilloma virus and HZ vaccines. Brydak and colleagues found that 57 persons of the elderly population would have to be vaccinated to prevent a single case of influenza. They interpreted their findings by stating that the funding of routine influenza vaccination programmes would be a very cost-effectiveness approach in this population [5]. Hillemanns and colleagues reported that a total 120 girls would have to be vaccinated to prevent a single case of cervical cancer in Germany and considered the HPV vaccination programme to be a cost-effective strategy when compared to cervical screening alone [21]. Finally, a cost-effectiveness evaluation of HZ vaccination in reducing HZ (shingles) and PHN in the elderly in Belgium has found that NNV is 12 in order to prevent one case of HZ; while it is 35 for PHN. It was considered as a cost-effective strategy in Belgium to vaccinate elderly aged 60 years and older [16].

De Serres et al. estimated that 314,000 to 2.7 million persons would have to be vaccinated to prevent a single case of rabies acquired through bedroom bat exposure. Furthermore, 293–2500 health care providers would have to be vaccinated to prevent a human case of rabies in the same setting. This study suggested that the extensive resources required to prevent a single case of rabies through post-exposure prophylaxis would be higher than what would be considered reasonable [30].

3.3. Modelling designs

Two studies have used modelling simulations to calculate NNV to estimate the impact of vaccination programmes. Using a mathematical model Brisson et al. were able to calculate the NNV required preventing HPV-associated outcomes and death. Their findings suggest that among 12-year-old girls, eight are required to be vaccinated to prevent a single case of genital warts. Similarly, 324 girls would have to be vaccinated to prevent a single case of cervical cancer. It is important to mention that these numbers were calculated assuming that the HPV vaccine provides lifelong protection with 95% vaccine effectiveness. Based on their mathematical models, the authors suggested that the current HPV immunization programme could reduce the number of cases with genital warts and cervical cancer [19]. In another study, Van Rie and Hethcote applied computer programmes to compute NNV to estimate and compare the effectiveness of five different immunization strategies. They found that NNV to prevent a case of pertussis was lowest for the adolescent strategy, while the cocoon strategy had the lowest NNV to prevent a single case in young infants [24].

4. Discussion

The NNV is often equated to the number-needed-to-treat (NNT) metric, commonly used in assessing the effectiveness of a healthcare intervention. We searched the literature to identify how scholars utilized this metric and focused on the recommendations and conclusions drawn from these studies. Broadly, NNV has been used in the literature to describe three main domains: potential impact of a given vaccination programme, cost-effectiveness and economic analyses, and modelling studies to compare different vaccination strategies.

Researchers who calculated NNV to demonstrate potential benefits of particular vaccination programmes based their calculations on risk difference or other similar formulae. Authors attempted to compute NNV across different health endpoints [7,17,20], compare different types of vaccines [6], estimate vaccination impact in immune-compromised populations [8,11], assess the effect of repeated vaccinations [9], and describe patient and physician expectation about NNV [18]. As expected, most of the conclusions drawn from this group of studies reported that vaccination programmes that require a lower NNV are more beneficial in comparison to programmes that necessitate higher NNV.

The second group used health economics to assess the cost-effectiveness of different vaccination programmes. Some studies used NNV as a metric to demonstrate the cost-effectiveness of a particular vaccination programme and use this information to make a policy recommendation, while other studies reported high costs based on NNV calculations, challenging specific vaccination programmes that were found to be resource intensive. The third group used mathematical modelling and computer simulations to calculate NNV to determine the benefits and impact of different vaccination strategies and health outcomes [19,24].

NNV estimates varied widely between publications, likely relating to the fact that they are complex to calculate and are dependent on several factors, including setting, population, disease prevalence, and the healthcare system in question. As a result, NNV estimates are most relevant to the specific study group for which they are calculated, with a limited capacity for broader application. While this may be useful in some circumstances, such as calculating cost effectiveness of two candidate vaccines for a specific population, this brings into question whether NNV is an appropriate measure for use in public health. Few of the papers we reviewed fully acknowledge the limitations of NNV, reinforcing the need for caution and more agreement on when and how it is appropriate to use this metric.

NNV is thought to be an intuitive measure of the effectiveness of vaccination comparable to NNT. However, this comparison has not been evaluated and may not be valid. When the NNT is used to evaluate drugs, the direct costs and benefits to the individual are much clearer, may apply to a shorter time period and occur in close temporal relationship to exposure. This is not the case for NNV, since vaccinations are preventative, effects may be indirect, and the extent and exact timing or extent of exposure is often unknown. Kelly et al. argue that NNV is considered on an annual basis because vaccine preventable diseases tend to have a short incubation period, a short course, and may recur [4]. However, most vaccination programmes are expected to carry on preventing cases over several years, revealing another limitation to NNV. Furthermore, once diseases are approaching elimination, the NNV becomes very large and even misleading, since immunization cannot stop at that point.

These limitations were recently highlighted in a study that attempted to utilize NNV in mathematical models to calculate the indirect effects of vaccines, such as reduction in secondary cases due to fewer transmissible cases and the benefits of herd immunity. The study criticized the use of standard NNV calculations, finding that they tend to produce overestimated numbers when compared to dynamic NNV calculations that incorporate the indirect effects of the immunization programmes. The study concluded that standard NNV calculations undervalue the potential benefits of vaccination programmes and should therefore be used and interpreted with caution [31]. Dynamic mathematical models are established essential tools for assessing the need and potential impact of vaccines, including their indirect effects. Such models are however labour intensive and hard for non-modelers to understand. NNV is a simpler measure, but its limitations used in isolation of more sophisticated approaches need to be emphasized.

In conclusion, NNV has been used in a wide variety of ways in the literature: to justify immunization programmes, to evaluate public health or economic benefits or to compare immunization strategies. Its simplicity make it an appealing measure. However, methods for calculating NNV lack uniformity and there are no defined thresholds for what is a favourable NNV, making interpretation and generalizability of this measure difficult. Furthermore, the NNV does not take into account the indirect effects of vaccination, and so should be used with caution. Further discussion is required in order to reach a consensus on the appropriate use of NNV in evaluating vaccination programmes.

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Conflict of interest statement

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