Bayesian versus frequentist methods for estimating true prevalence of disease and diagnostic test performance

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ARTICLE INFO

Article history:
Accepted 4 August 2014

Keywords:
Bayesian methods
Frequentist methods
Diagnostic test performance
True prevalence
Sensitivity
Specificity

Introduction

As the two main schools of statistical reasoning through which inference to the population is made by analysing data and incorporating uncertainty of measures, Bayesian and frequentist philosophies have been used to estimate diagnostic test performance and the true prevalence of diseases. However, controversies exist between the two philosophies, such as the use of fixed parameter values in the frequentist approach or the inclusion of prior information in the Bayesian approach. So, is the philosophical debate between these two approaches still relevant for such practical questions?

The Bayesian philosophy arose from a statement made by the Reverend Thomas Bayes (1702–1761), a British mathematician and theologian, who was the first to apply statistical probability inductively. According to Bayes, ‘all forms of inference are based on the validity of their premises’ and ‘no inference can be known with certainty’ (Thrusfield, 2005). In 1814, the French mathematician, Simon-Pierre Laplace published a mathematical description based on Bayes’s idea (Gelman et al., 2004). In the Bayesian philosophy, scientific observations do not exist in a vacuum and information available prior to making a series of observations influences the interpretation of those observations (Thrusfield, 2005).

Bayesian analysis can be regarded as a process of adjusting and updating the likelihood of an event based on data. Thus, population parameters, such as sensitivity (Se) and specificity (Sp), are assumed to have a probability distribution representing our prior knowledge of their values. This information is combined with observed factual field data in a model for estimation (Speybroeck et al., 2012a). For Bayesians, a parameter is assumed to have an intrinsic probability distribution with a 95% credibility interval (Gardner, 2002). Thus, Bayesian principles are often applied in order to estimate disease prevalence and test characteristics, especially when there is no gold standard (Enne et al., 2000; Branscum et al., 2005; Rutjes et al., 2007; Meyer et al., 2009).

The frequentist philosophy emerged in the 20th century with the works of Fisher (1922) and Neyman and Pearson (1928a,b), who enunciated the concept of relative frequency (Vallverdú, 2008). This concept sustains the idea that a probability is a frequency determined from an experiment repeated a large number of times. Frequentist statisticians attempt to draw conclusions by focussing primarily on results obtained from experiments or samples. In the frequentist reasoning, a parameter is a fixed value with a 95% confidence interval derived from the sample. It is assumed that this 95% confidence interval would contain the true value of the parameter 95% of the time if the estimation were repeated a large number of times.

Therefore, Bayesian philosophical methods are based on the idea that unknown quantities, such as population means or proportions, have a probability distribution that expresses our prior knowledge or belief about such quantities, before we add the knowledge gained from observational data. Bayesian inference considers the data to be fixed and parameters to be random, because they are unknown. In frequentist
Estimating the true prevalence of disease and diagnostic test performance with imperfect tests

The ability of a diagnostic test to distinguish correctly truly diseased from non-diseased individuals, when applied to a randomly chosen population, is necessary so as to understand the epidemiology of the disease, to implement disease control programmes and to evaluate new diagnostic tests (Greiner and Gardner, 2000; Lewis and Torgerson, 2012). Mathematically, the estimation of test performance parameters is essentially the same question as estimating true prevalence (Lewis and Torgerson, 2012). The true prevalence (the proportion of truly diseased individuals in the population of interest) is also an essential parameter required to appraise the impact of a disease in a population of interest and to prevent biased estimations of disease burden (Dohoo et al., 2003; Speybroeck et al., 2012a).

The accuracy of estimation of true prevalence depends on the performance parameters of the test(s) to be applied (Horst et al., 2007). Among performance indicators of a diagnostic test, Se and Sp are the most commonly used. Test Se or Sp indicates the probability that a truly infected or uninfected individual yields a positive or negative test result, respectively. Ideally, Se and Sp values for a given test should be estimated from a reference population with a clearly identified status determined by historical (accurate) information or, more commonly, by a relevant gold standard (Se = 1 and Sp = 1) that is able to discriminate infected/diseased individuals from uninfected/non-diseased individuals in a population (Dohoo et al., 2003). When such a perfect test exists, an estimation of performance parameters of the new test, as well as true prevalence, can be done easily (Rogan and Gladen, 1978).

In practice, such a test is hardly ever available, given that the diagnostic performance of a test is influenced by a number of endogenous and exogenous factors (Rutjes et al., 2007). As an alternative, a combination of multiple imperfect tests (Se < 1 and/or Sp < 1) may be used to estimate disease parameters (Black and Craig, 2002). With multiple tests, overall misclassification errors are reduced and are expected to be lower than with a single imperfect test.

For example, the isolation and identification of Brucella spp. is considered as the reference standard method; a positive test result provides an unequivocal diagnosis of a positive case of brucellosis (World Animal Health Organisation, 2009). However, these methods are not always feasible in diagnostic investigations. Therefore, diagnosis must be based on imperfect serological methods, such as the Rose Bengal test (RBT) and the indirect ELISA (iELISA), which are the two OIE prescribed tests for trade and are commonly used in combination for the diagnosis of brucellosis (Nielsen, 2002; Saegerman et al., 2004; World Animal Health Organisation, 2009; Godfroid et al., 2010; Sanogo et al., 2013).

Estimation of true disease prevalence and test characteristics with combined imperfect tests poses challenges, including (1) potential misclassification errors, (2) possible dependence between tests, and (3) sparseness of data (Cowling et al., 1999; Dohoo et al., 2003; Messam et al., 2008). Both Bayesian and frequentist approaches have been proposed to tackle these challenges.

Estimation with a single test

In the simple case, where a single imperfect diagnostic test is applied in a population of interest, a total of three parameters must be estimated, whatever the method, namely, Se, Sp and true prevalence. In this case, the apparent prevalence (the proportion of positive test results) is the only information given by the data. From a frequentist perspective, estimation can be done only if fixed external information is provided on the values of Se and Sp, but this is difficult, since test properties are known to be context-specific and cannot realistically be assumed to be fixed and known in advance, such as the values given by the manufacturer of a test (Thrusfield, 2005).

As far as external information has to be included for estimations, Bayesian methods seem to be more helpful in obtaining acceptable and realistic results, since they offer the possibility of including the known uncertainty with respect to diagnostic test characteristics, while testing whether data conflict with prior information (Joseph et al., 1995; Berkvens et al., 2006; Speybroeck et al., 2012b). However, the accuracy of Bayesian estimates is dependent on the availability and quality of prior knowledge, which may be a limiting factor and may also conflict with frequentist philosophy.

Estimation with more than one test

When a combination of at least two tests is used, the test results for a given individual could be interpreted either in series (only animals that test positive to both tests are considered to be test positive) or in parallel (animals that test positive to one test, to the other test or to both tests are considered to be test positive) (Black and Craig, 2002). A combination of tests may also result in dependence or correlation between the test results. As a consequence, either conditional independence or conditional dependence assumptions need to be made for accurate estimation of disease prevalence and test properties (Jones et al., 2010).

Conditional independence implies that the results of the second test (T2) do not depend on whether the results of the first test (T1) are positive or negative among infected (or uninfected) individuals (Enae et al., 2000; Gardner et al., 2000). If we consider the skin test or the iELISA, two tests referred to above for the diagnosis of brucellosis, conditional independence is likely to exist in relation to their respective targets (cellular response for the skin test and humoral response for iELISA), especially in a low prevalence context (Saegerman et al., 1999). In this case, calculation of test Se and Sp will depend mainly on the testing strategy adopted (in parallel or in series) (Dohoo et al., 2003).

Mathematically, assumptions such as conditional independence and a constant prevalence over sub-populations are needed to estimate prevalence (Enae et al., 2000). These assumptions are necessary so as to reduce the number of unknown parameters to be estimated (Berkvens et al., 2006), Gart and Buck (1966) and Staquet et al. (1981) proposed frequentist methods assuming conditional independence between a new test and a reference test with known Se and/or Sp. However, test Se (stage of infection) and Sp (similar immunogenic component) values are influenced by the characteristics of the population in which the test is applied (Saegerman et al., 2004; Berkvens et al., 2006) and cannot be considered as intrinsic constant and known parameters (Thrusfield, 2005). Moreover, assuming fixed values might not be realistic, since many factors, such as the presence of cross-reacting agents (Saegerman et al., 2004) and low infection pressure, may influence test parameter values (Speybroeck et al., 2012b).

Hui and Walter (1980) proposed another major frequentist method to deal with the case where Se and Sp values of the reference test are unknown. In addition to an assumption of conditional independence, this approach required testing at least two populations with distinct prevalences of disease, but constant Se and Sp (Hui and Zhou, 1998; Enae et al., 2000; Dohoo et al., 2003). The approach was extended to
cover other settings, including cases with more than two tests and multiple populations (Walter and Irwig, 1988; Johnson et al., 2001). The accuracy of estimates made with these methods also relies on the assumption of a large sample size (Enøe et al., 2000; Pouillot et al., 2002; Berkvens et al., 2003; Pouillot, 2003). Toft et al. (2005) provided a useful overview of possible pitfalls when using this paradigm, especially the assumption of conditional independence, which is not always satisfied in practice (Gardner et al., 2000; Dendukuri and Joseph, 2001; Branscum et al., 2005; Berkvens et al., 2006).

Testing situations handled by the frequentist models of Cart and Buck (1966), and the case of unknown Se and Sp already covered by the model of Hui and Walter (1980), have also been examined under the Bayesian framework. Joseph et al. (1995) proposed a Bayesian model for estimation with no constrained parameters and assuming conditional independence. Numerically, this model appeared to be approximately equivalent to the frequentist approach (Dendukuri and Joseph, 2001). Nevertheless, even if estimation was possible with this latter model, inclusion of information on the uncertainty of parameters to be determined is required to get realistic and meaningful estimates (Enøe et al., 2000).

Conditional dependence particularly occurs when combined tests target a similar biological phenomenon, such as the presence of immunoglobulins (Igs) (Gardner et al., 2000; Dendukuri and Joseph, 2001). Thus, conditional dependence is likely to exist between the RBT and IELISA, two assays ostensibly targeting similar anti-Brucella antibodies. However, the RBT detects the presence of IgG1 (IgG2 and IgM also have some agglutination activity), while the IELISA targets IgG and/or IgM, depending on the conjugate used (Nielsen, 2002; Sægerman et al., 2004, 2010; Sanogo et al., 2013). In this scenario, calculation of test Se and Sp under conditional independence is adjusted by the inclusion of the covariance factor expressing the extent of the dependence among positive and negative results, and by taking the testing strategy into account (Dohoo et al., 2003).

When dependence is present, estimates should be adjusted by considering biological and technical mechanisms giving rise to the test results and by including the extent of the dependence between them (Pepe and Janes, 2007). With two correlated tests, a total of seven parameters have to be estimated instead of five under conditional independence (e.g. two sensitivities, two specificities, two covariances and the true prevalence), and the dependence needs to be accounted for (Berkvens et al., 2006; Praet et al., 2006). Some frequentist methods require the application of at least two tests to allow estimation of parameters of interest (Dendukuri and Joseph, 2001). Such an approach might be impractical when tests are expensive, time consuming or invasive.

Instead of using results from at least two tests in order to allow estimation of disease parameters, Bayesian modelling offers an alternative option to obtain estimates of the true prevalence of disease, and test Se and Sp, while accounting for conditional dependence (Qu and Hagdru, 1998; Gardner et al., 2000; Dendukuri and Joseph, 2001; Georgiadiis et al., 2003; Sanogo et al., 2013). However, informative priors are needed for at least four of the parameters of the model: two sensitivities, two specificities, two covariances and the true prevalence.

Bayesians versus frequentist methods

Previously, Bayesian approaches were difficult to apply because of major mathematical and computational requirements, but have been facilitated by the application of Markov chain Monte Carlo (MCMC) methods and the availability of high quality statistical software packages, including JAGS (Plummer, 2003), WinBUGS (Lunn et al., 2000) and OpenBUGS (Lunn et al., 2009). These are now the tools of choice in many areas of application and appear to offer practical advantages over their frequentist counterparts (Greiner and Gardner, 2000; Dunson, 2001; O’Hagan, 2004). Bayesian methods facilitate estimates of population parameters by combining additional knowledge and likelihood in the same model. Uncertainties of reference tests with respect to Se and/or Sp, expressed as probability distributions, are combined with observed field data to produce posterior probability distributions of true prevalence and test performance (Speybroeck et al., 2012b). Compared to frequentist methods, Bayesian methods also offer more options and flexibility so as to derive the best possible estimates of parameters in realistic settings. When two imperfect tests are used, conditional dependence can be addressed in a Bayesian framework by running both models with conditional independence between tests given true disease status, and those with conditional dependence, then checking the robustness of the parameters or using model selection criteria, such as the deviance information criterion (DIC) (Berkvens et al., 2006; Dendukuri et al., 2010). Robustness of estimates should also be checked systematically across a range of plausible values based on the evidence to date (Enøe et al., 2000; Speybroeck et al., 2012a).

A systematic review and/or quantitative reviews summarising data using appropriate meta-analytical methodologies are preferred in order to obtain informative priors on diagnostic test performance (Irwig et al., 1995; Dohoo et al., 2003; European Food Safety Authority, 2009). Application of evidence-based medicine and the quality assurance of the process used to obtain prior information are important in assessing the quality of the approach. In the case of emerging infectious diseases, where prior information may not be available, non-informative priors might be used. When no informative prior knowledge is included in the estimation process, the results of frequentist and Bayesian analyses are similar (Enøe et al., 2000; Dendukuri and Joseph, 2001).

Whatever the priors, a sensitivity analysis of prior information should be undertaken to assess its potential influence on estimates (Menten et al., 2008; Sanogo et al., 2013). Special care should be given to the selection of available information in order to obtain unbiased estimates (Spiegelhalter et al., 2002; Berkvens et al., 2006). The procedure for incorporating available knowledge or prior information into the model, and the mathematical issues, have been described previously (Enøe et al., 2000; Gardner et al., 2000; Dendukuri and Joseph, 2001; Branscum et al., 2005; Berkvens et al., 2006).

In addition to the challenges relating to misclassification bias, the representativeness of data regarding the population of interest and the quality assurance of the process (traceability) are two key issues to be considered in both approaches. Thus, different stages of the disease and the age of the animals should be considered, and an appropriate sampling strategy used to compose the reference population and, consequently, to minimise sampling error and biased posterior estimates. Consequences of using imperfect tests should be accounted for at the analysis stage (as well as the planning stage) of the estimation process.

Conclusions

Controversies between the frequentist and Bayesian approaches are more a philosophical than a practical issue. Although originating from different statistical philosophies, Bayesian and frequentist approaches are two methodological options to deal with test performance and true prevalence estimation. While the frequentist approach concentrates only on likelihood-based estimation, the Bayesian approach uses the likelihood and prior information for estimation. Both approaches have proposed solutions to address challenges related to estimation of test performance and true prevalence, taking into account field conditions. Whatever the approach used, it is necessary to ensure that appropriate assumptions related to the application of a given approach hold.
Acknowledgements

The authors would like to thank the Institute of Tropical Medicine of Antwerp and the University of Liège, Belgium, for academic support.

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