



Role of infectious disease information system and risk assessment in control of livestock diseases in Indian perspectives: A review

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ABSTRACT

Many livestock diseases have a severe impact on the country's economic status. Diseases cause highly destructive epidemics. It imposes severe consequences, especially in the areas of densely populated livestock. Infectious Disease Informatics, an emerging field of study, involves information management in a systematic way and analysis of issues related to infectious disease detection, prevention and management. Surveillance and awareness are the two essential phenomenon to be adapted, so that the early detection of disease outbreaks is possible and rapid control measures are schemed to prevent further spread of the disease. Recent advances in disease surveillance system, information technology and epidemiological modelling have raised the expectations on the early warning systems as they are not only sensible but also necessary tools to combat the re-occurrence and spread of infectious diseases. The evolution of remote sensing instrumentation, GIS technology and their application and evaluation of satellite data to the issues of disease risk prediction are reviewed and discussed. The importance of risk assessment and disease risk prediction in livestock epidemiology has been illustrated with example case studies. An overview of the types of epidemiological studies, various sampling techniques and the role of meta-analysis in livestock disease informatics has been specified. The paper also focuses on the techniques being developed for infectious disease risk prediction in both space and time.

Key words: Disease informatics, Disease modelling, Infectious disease, Livestock diseases, Risk assessment

Disease informatics is defined as the application of information science in dealing with the diseases with least error, identifying a number of targets to combat a group of diseases and designing a coherent solution for the problem (Zeng *et al.* 2005). Infectious disease informatics is an emerging field of study that includes information management in a systematic way and analysis of issues related to infectious disease detection, prevention and management. Scientists, farmers, clinical researchers, epidemiologists and public health personnel contribute to the field of disease informatics and in turn benefit from it. The information generated using different techniques of disease informatics will pave the way for designing of disease control and prevention mechanisms.

Traditional approach

The collection of infectious disease data, distribution, and reporting is a paper-based process that involves telephonic conversations for data transmission and entering or updating paper-based case report forms by multiple

personnel. This approach involving the information processing is hard and laborious.

The knowledge of various symptoms of rarely encountered exotic diseases and different risk factors involved is essentially to be understood by farmers and veterinarians. An effective surveillance is one in which there exists a close association between farmers and veterinarians, and between veterinarians and the Veterinary Service systems of the state. Farm animal disease surveillance is a much needed aspect to be strengthened. The poor understanding of the spread of highly infectious exotic diseases locally remains a main issue. This requires a targeted research initiative having a clear aim of improving the standards of bio-security at the farm level.

Current scenario

A wide range of statistical and analytical models targeted at the analysis of disease data for surveillance and outbreak prediction, is being adopted rapidly to meet the critical purpose of effective detection, prevention and management of the outbreaks of infectious diseases of plants, animals, and humans.

At present infectious disease information systems provide very limited support to professionals in the analysis of data and developing models for disease prediction. An integrated domain is critically needed which offers the

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capability to serve the purpose of advanced spatio-temporal data collection and analysis, geo-coding, predictive modelling, and visualization. An information system where data is integrated from the process of collection to the point of modelling and visualization analysis would lead to much better quality of the data input, more timely analysis, better prediction of outbreaks, and potentially upgraded disaster management.

Disease modelling

An epidemiological model is defined as a mathematical and/or a logical representation of the epidemiology of a disease and the processes associated with the disease transmission. These models quantitatively provide a representation of the transmission dynamics of animal diseases in time and/or space among individual animals and/or animal groups (Garner *et al.* 2011). A model therefore enables the efficacy evaluation of potential control measures and estimates the magnitude of the future, duration and topographical extent of an outbreak when the applications of specific control measures are provided (Willeberg *et al.* 2011, Saegerman *et al.* 2011).

The diffusion of an infectious disease involves properties of the agent, the host and the environment in which transmissions take place (Wilson *et al.* 2007). Epidemiology brings about the understanding of the infectious diseases behaviour, impacts and possible predictions in future about its distribution. The purpose of modelling infectious diseases, is the evaluation of the agent-host-environment interface and efforts to alter the common space through intervention for our advantage (Chute *et al.* 2008).

Models in epidemiology can be classified into different categories depending on their uncertainty (deterministic or stochastic) and chance, treatment of variability, space (spatial or non-spatial), time (continuous or discrete intervals), and the population structure (homo or heterogeneous mixing) (Young 2008). The application of these models can be found in three main groups like the models for planning surveillance, models for interpreting surveillance data as part of ongoing control or eradication programmes and the models for evaluating the performance of surveillance systems (Reeves *et al.* 2011).

Mathematical models: Mathematical models are the important tools in the analysis of the spread and control of infectious diseases. The formulation process of the model made the assumptions, variables, and parameters clear; models provide visionary results such as basic reproduction numbers, contact numbers, replacement numbers, thresholds, herd immunity and percentage of animals requiring vaccination (Herbert 2000).

These compartmental models (Hoppensteadt 1982) consider the population of several classes, viz. susceptible $S(t)$, infected $I(t)$, exposed $E(t)$, passive immunity from its mother $M(t)$ and removed $R(t)$. $S(t)$ represents those individuals susceptible to the disease or the number of individuals not yet infected with the disease at time t . $E(t)$ gives the exposed or latent period of the disease. $I(t)$ denotes

the number of individuals who are infected with the disease and enable the disease spread to those in the susceptible category. $M(t)$ comes into picture when an individual is born with a passive immunity from its mother. $R(t)$ represents those individuals who are infected and then removed from the disease category, either due to immunization process or due to death. Those individuals in this category are not able to be infected again or to transmit the infection to others.

Basic reproduction number (R_0): The basic reproduction number, is considered as the most important quantity in mathematical epidemic or disease transmission theory, where its value dictates whether a large epidemic outbreak can occur or not (Damian *et al.* 2008). The basic reproduction number, represented as R_0 , can be given as the expected number of secondary cases reproduced by a single infection in a population, which is completely susceptible. It is very important that R_0 is a dimensionless quantity and not to be taken as a rate quantity, which have units of time^{-1} ,

$$R_0 \propto \frac{\text{Infection}}{\text{Contact}} \cdot \frac{\text{Contact}}{\text{Time}} \cdot \frac{\text{Time}}{\text{Infection}}$$

and can be given specifically as

$$R_0 = \Gamma \cdot c \cdot d$$

where, Γ transmissibility i.e., the probability of infection when the contact between a susceptible and infected individual is given; c , the mean rate of contact between susceptible and the infected individuals, and d the duration of infectiousness.

This measure helps to determine whether an infectious disease can spread throughout a population or not. When, $R_0 < 1$, the die out of the infection in the long run and $R_0 > 1$ implies the ability of the infection to spread in a given population.

The more the value of R_0 , the harder it becomes to control the spread of the infection. The proportion of the population that needs to be vaccinated to prevent sustained spread of the infection, for a 100% effective vaccine, can be given by $1-1/R_0$. Several factors affect the quantity R_0 which includes the duration of infectivity of affected animals, the number of susceptible individuals in the population with those the affected patients are in contact with and the extent of infectiousness of the organism (Adler 1992).

For behaviourally distinct individuals or groups, the process of averaging the mixing patterns can be adapted. With a symmetric transmission between groups, this process of averaging decrease the basic reproduction ratio R_0 or leave it unaltered in the epidemiological models (Khan *et al.* 2014).

Stochastic models: Stochastic models are the empirical models for the counts of an infectious disease and mainly taken into action for one or more of the reasons including identification of potential risk factors, surveillance and monitoring, description of the disease and prediction of the disease, forecasting or forewarning of disease. These models have to deal with a particular characteristic of the disease

counts, the most questionable being the time period of infection (Nielsen *et al.* 2011).

Models such as Periodic regression, Logistic regression, Log-linear models, count models and Structural equation models are used to assess the significance of the risk factors for disease incidence or an outbreak as well as prediction and forecasting (Valerie Isham 2004).

Periodic regression: The method of periodic regression is simple and flexible and is used for the detection of seasonal and cyclical pattern in a time series data analysis. There are kinds of agricultural or disease outbreak data that tend to oscillate up and down at regular intervals of time showing a detectable periodic character. A periodic or cyclic behaviour of many natural environmental phenomena is expressed in time and space (Cobanovic 2006).

Seasonal variations are an important characteristic of many biological and agricultural series. Periodic events are not only close to the biological data, but also to non-biological data. Most of the cyclical and seasonal variations of different types of data occur depending on the daily, monthly, yearly changes. Periodic and cyclic variations can be identified in a number of investigated problems in both biology and agriculture (Bernard 1999).

A periodic trend is a curve that is repeated at fixed time intervals and which relates some variable to time. It is

known as a Fourier curve and is useful for any type of data that tend to oscillate up and down at regular intervals of time. *Peste des petits ruminants* (PPR) is a highly contagious disease of small ruminants that is highly endemic in India (Raghavendra *et al.* 2008). The periodic regression employed on PPR is shown in Figs 1, 2 to understand the periodic and cyclical pattern over the 14 years.

Elements of Disease mapping - Understanding transmission dynamics

Geographical information system (GIS) and spatial analysis: A geographical information system (GIS) is a computerized system that deals with the combination of descriptive and spatial data for mapping and analysis. The ability to integrate different types of spatial data is the main strength of a GIS (Hendrickx *et al.* 2004). It can be used to map the available disease information and relate it to the known factors that influence the distribution of these infectious diseases, such as climate and other environmental factors. It is used to accompany the techniques of modelling and traditional ecological monitoring, and paves a way to depict the complex relationships in the disease ecology (Simon Brooker *et al.* 2002).

Spatial analysis in connection with GIS is described as the ability to alter the spatial data into different forms and

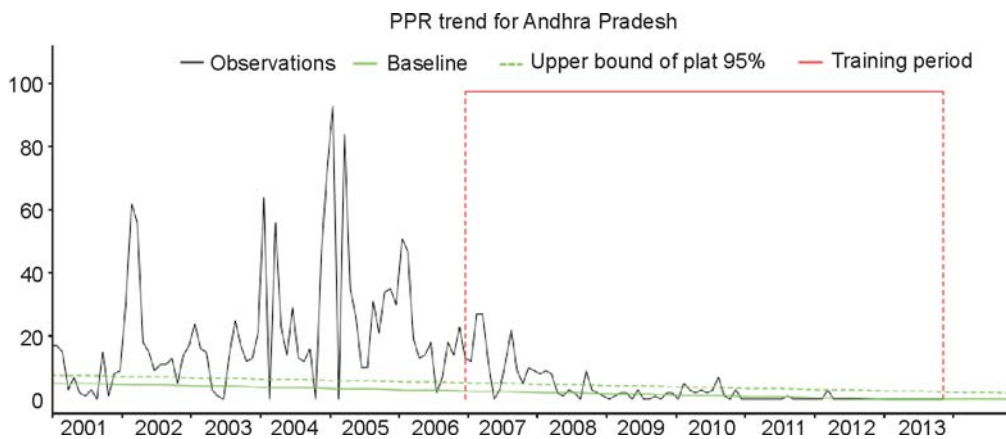


Fig. 1. The periodic regression curve of PPR outbreaks in Andhra Pradesh resulted from the real data during 2001-2013.

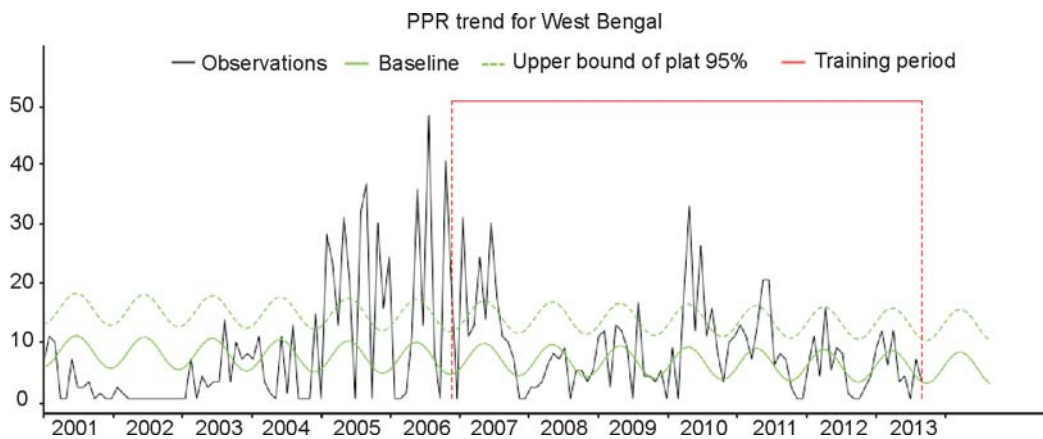


Fig. 2. The periodic regression curve of PPR outbreaks in West Bengal resulted from the real data during 2001-2013.

derive additional meaning. In the context of spatial epidemiology, one can differentiate between three tasks of spatial analysis namely exploratory data analysis, visualization/mapping and modelling.

Hot spot analysis: Hot Spot Analysis is a detection method of the spatial clusters which distinguishes the statistically significant spatial concentrations of the high and low values associated with a set of geographic features (Cringoli *et al.* 2004). The Hot Spot Analysis tool in Arc GIS uses the mechanism of Getis- Ord G_i^* algorithm. The Getis- Ord local statistic is given as:

$$G_i^* = \frac{\sum_{j=1}^n W_{i,j} X_j - \bar{X} \sum_{j=1}^n W_{i,j}}{S \sqrt{\frac{n \sum_{j=1}^n W_{i,j}^2 - (\sum_{j=1}^n W_{i,j})^2}{n-1}}}$$

where x_j gives the attribute value for feature j , w_{ij} is the spatial weight between feature i and j , n represents the total number of features and:

$$\bar{X} = \frac{\sum_{j=1}^n x_j}{n}, S = \sqrt{\frac{\sum_{j=1}^n x_j^2}{n} - (\bar{X})^2}$$

The output of a Hot Spot Analysis is a p -value and a Z score for each feature. These values represent the significance of the spatial clustering of values statistically, given the scale of analysis (distance parameter) and the theory of spatial relationships.

A small p -value and high Z score for a specific feature indicate a spatial clustering of high values. A small p -value and a low negative Z score indicate a spatial clustering of

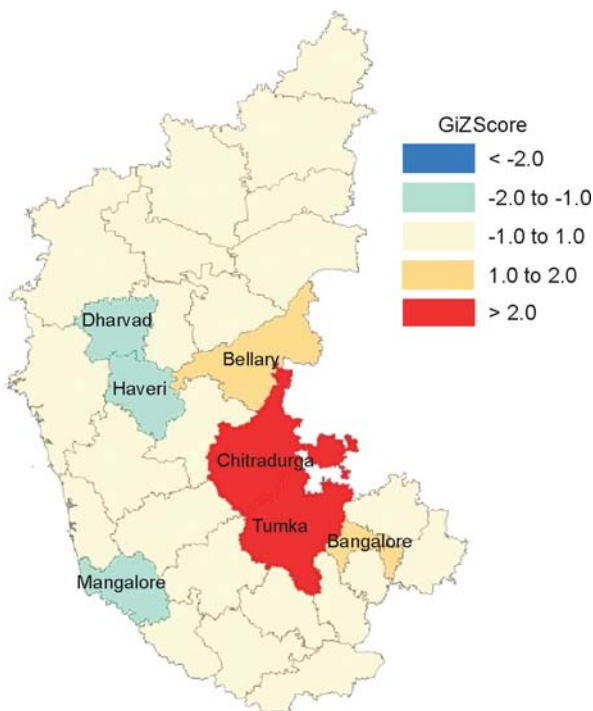


Fig. 3. Hot Spot Analysis using spatial statistics with rendering for PPR outbreaks in Karnataka during 2000-2013.

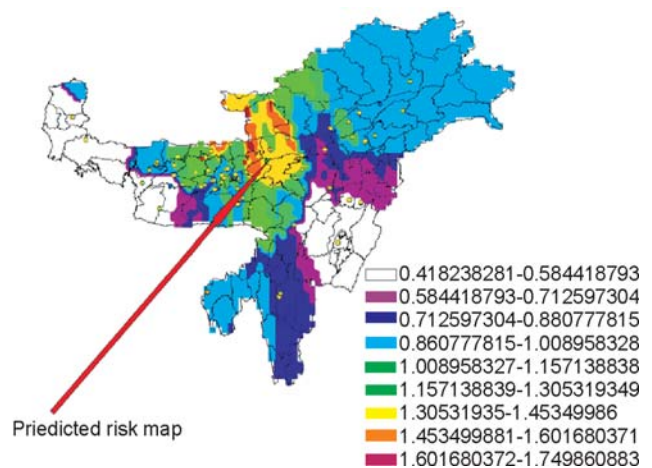


Fig-4- GIS Based Kriging Interpolation for CSF using NDVI and LST (satellite data).

low values. The more the Z score the more intense the clustering. A near to zero Z score indicates no evident spatial clustering. The basis of Z score is the Randomization Null Hypothesis computation. Hot spot analysis on PPR outbreak data in Karnataka state was performed to identify the significant clusters (Fig. 4).

Risk mapping: Risk maps are fundamental for estimating the scale of the risk, and hence the resources needed to combat a particular disease. They provide benchmarks for assessing the progress of control and indicate which geographic areas should be prioritized. To interpret the design of risk-based surveillance activities, the risk map generated by the predictive model can be used. It operates by identifying the high-risk point locations indicating where to prioritize epidemiological surveillance and control activities (Angel Ortiz-Pelaez *et al.* 2010).

Visualization/mapping can be used in varied ways to investigate the results of traditional statistical approaches that have been dealt with a powerful statistical analysis software. With respect to the applications of GIS, the primary visualization mechanism involves the map, which can assist the display for policy and strategic planning and guide the validation of model prediction (Adrian Treves *et al.* 2011).

$$\text{Risk} = (\text{Elements at risk}) * (\text{Hazard}) * (\text{Vulnerability})$$

Hazard (H) is the probability of occurrence of an effective damaging natural event within a specified time period and within the given area. Element at risk (E) includes the population, public services, economic activities, infrastructures and utilities etc., at risk in the given area. Vulnerability (V) is the subjection of a given element or a set of elements at risk resulting from the occurrence of a damaging event of a given significance. Risk (R) is the degree of loss expected due to a particular natural event. It is expressed as the product of hazard (H), vulnerability (V), and the element at risk (E).

The risk map are created by encrusting the vulnerability and hazard maps. The risk mappers of next generation adapt several criteria for the selection of a model, validate the

model predictions hence finally including predictors from organism biology along with the predictors of human and environment. Risk maps can also be used to display the patterns of drought, conflict and other related events (Bartolomeo *et al.* 2004).

Kriging: In geo-statistics, *Kriging* is the method of optimal interpolation based on regression against the observed *z* values of associated data points, weighted according to prior spatial covariance values. Kriging of CSF incidence in NER region of India with co-variables like NDVI and LST (Remote sensing data) was employed (Fig. 5)

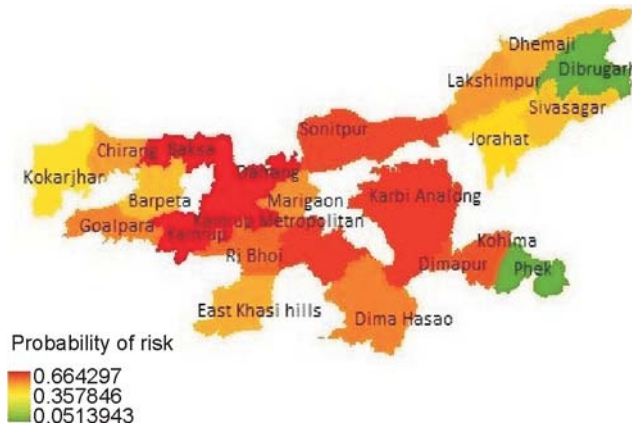


Fig.5. Risk map depicting the probability of occurrence of CSF outbreaks in North East Region of India.

Development of risk map using remote sensing (RS) and GIS

Remote sensing (RS) refers to acquiring the information of an object or event, by means of an aircraft or a satellite (Bartolomeo *et al.* 2004). Data generation using remote sensing uses a part of the electromagnetic spectrum. It records the electromagnetic energy emitted or reflected by the surface of the earth. The quantity of radiation from an object is influenced by both the properties of the radiation hitting the object and the object itself (Gao 1996).

In the case study, the risk map prediction for CSF in North Eastern regions was attempted using the Remote sensing applications and GIS. For this purpose, data viz. Land Surface Temperature (LST), and Normalized Difference Vegetation Index (NDVI), Distance from major cities (km), Distance from Highways (km), Distance from Roads (km), Distance from Railways (km), Distance from Water bodies (km), Rainfall were measured using earth observatory satellite images or maps. Using ArcGIS tool the raster layers are generated for each risk factor mentioned above. The Logistic regression model was employed for the risk map generation.

$$Y = \frac{1}{(1+e^{-(-0.088-0.002* \text{Distance from cities}+0.0001* \text{Distance from Highways}.....1.432* \text{NDVI})})}$$

The high risk of disease occurrence was predicted in Baksa, Darrang, Kamrup Metropolitan and Kamrup districts

of Asom with a probability of occurrence of 0.6643. A moderate to low risk was predicted in the other areas of North East Regions with a probability of occurrence of around 0.3578. A very low risk of disease occurrence was predicted in Dibrugarh district of Asom and Phek district of Nagaland with a probability of occurrence of 0.0514. To conclude from the study, the risk maps can act as important epidemiological tools to measure the probability of occurrence of CSF outbreaks and may be used for risk prediction of any other diseases. The Predicted risk map for CSF incidence in North eastern region of India is presented in Fig. 5.

Risk assessment models (import risk analysis)

The degree of disease risk is assessed by the importing countries through a process of risk analysis and is represented by the introduction, proliferation, and inception of one or more diseases by importing animals and animal products (Asseged *et al.* 2012). The assessment of risks (Import risk) of livestock disease can be done both qualitatively and quantitatively. While qualitative risk assessment gives poor resolution of risk whereas quantitative risk analysis provides a definite value which defines the threat to the disease that can be obtained (Forde-Folle *et al.* 2011).

Steps involved in Risk Assessment can be grouped under the following categories (Forde-Folle *et al.* 2011):

Hazard identification: The import of goods was identified at the national level and threats were assessed via surveillance efforts and border security check measures adopted by the exporting countries.

Risk assessment: The different factors underlying the transport of poultry chain were studied like farm level and animal level factors.

Risk management and Risk communication: It involves the final process in risk handling and management.

A risk assessment model of quantitative type has been developed to determine the framework that could lead to the introduction and maintenance of AI virus via the importation of chicken meat, live birds and chicken by-products into the country. The probability of occurrence of the hazard was carried out using R-PERT software with Monte Carlo simulation involving 10,000 iterations. Data for prevalences were collected from the studies carried out and their probabilities were calculated using R-PERT software.

According to this Quantitative risk assessment (Table 1), the risk of introduction of Avian Influenza virus into India is as 24 units (0.88% of import) from Asian countries, 1363 units (0.36%) from European countries, 0.41 units (0.33%) from Australia and 613 units (0.76%) from North American countries. However, to provide an evidence, a number of prevalences from many Asian and American countries needs to be incorporated and a comprehensive approach using stringent strategies to break the chain of transmission of the virus in poultry will be needed for achieving the lasting disease control.

Types of epidemiological studies

There are three key approaches for an epidemiological study (Kenneth *et al.* 1998):

- Prospective studies, they are also called as cohort studies. They attempt to examine associations between the factors and the frequency of occurrence of a disease by comparing attack rates in groups of individuals in which the decisive factor is either present/absent, or its frequency of occurrence varies looking forward over a period of time.
- Retrospective studies, they are referred to as case-control studies. They attempt to compare the frequency of occurrence of a determining factor in diseased and control groups of individuals looking *backward* over a period of time.
- Cross-sectional studies, which attempt to examine and compare the approximate disease prevalence between varied populations and subsets of populations over a limited period of time.

Sample size and sampling frame in livestock disease control

Sample sizes: Sample sizes for estimating disease prevalence in large populations—

The general equation for sample size estimation can be given as:

$$n = P(100-P)/SE^2$$

Sample size (n) for controlling the standard error (SE) of estimate the prevalence for different values of the true prevalence (P) in large populations can be given by

$$n = \frac{P(100-P)}{[SE^2 + P(100-P)]/N^2}$$

A ready reckoner for the sample sizes required for estimating prevalence at different levels of absolute accuracy from large populations is given in the Table 2 (Putt *et al.* 1987).

Sampling frame: For any epidemiological study, sampling is the major prerequisite. Sampling should be robust, scientifically accepted and field level feasible. There is a general tendency to carry out sampling of livestock for epidemiological measurements assuming it to be 'random'. This may not be true representative sample of the target population. The process of sampling becomes more complicated if larger population, e.g., villages in a state, animals in a district, block, village or herd etc. It becomes much more complicated when multiple species are involved. Hence, scientifically feasible, strong sampling frame need to be developed for drawing random, representative and independent sample for epidemiological studies. A sampling frame is a list used to define a researcher's population of interest. The sampling frame defines a set of elements from which a researcher can select a sample of the target population. A researcher rarely has direct access to the entire population of interest in epidemiological research, hence, she/he must rely upon a sampling frame to represent the entire population of interest.

Sampling can be defined as the process of selection of

samples with appropriate size and characteristics. A sampling unit is the basic unit around which a sampling procedure is planned. A sampling frame is the list of all sampling units from a population (al-Sekait *et al.* 1992).

Samples from live animals can be collected from their blood, faeces, skin, genital tract and semen, eye, nasal discharge, saliva, tears and milk. The aim of sampling process is to avoid bias, which can be guaranteed by taking a sample randomly.

Population sampling in epidemiology can be done using various methods. The most commonly preferred techniques are random sampling, systemic sampling, multi-stage sampling and purposive sampling (Steven *et al.* 2004).

Random sampling: The basis of random sampling is that units selected are independent of each other and every unit in the population which is being sampled has exactly the same probability of being selected. This method of sampling removes bias in the sample selection and thereby removing one of the main sources of error in epidemiology studies.

The first step in random sampling is to construct a sampling frame, which is a list of all the individual sample units in the population. Each unit in the sample frame can then be assigned an identification number. A computer algorithm can be used to generate these random numbers. Then, the unit to be sampled is identified from the sample frame. From a random number table, random numbers are selected by starting anywhere in the table and which are then read either vertically down the columns or horizontally across the rows.

Systemic sampling: This method of sampling defines the process of systemically sampling a population i.e. every nth unit in that population is sampled, if a 1/n sample is required. If a 25% (1/4) sample is required, every 4th unit in the population is sampled.

Multi-stage sampling: This method is used for constructing sample frames of individual animal units. The first stage of this technique involves population sampling in different stages, with a different sample unit at each stage. Sometimes, constructing a sample frame of individual animals may not be possible. Then livestock herds, farms or villages can be considered as units. The sample units are then randomly selected from the resulted sample frame. After the sampling units have been selected, it may be possible to construct a sample frame of the animals within the unit, sampling these in turn.

As an alternative method, all the animals within a herd, farm or village can be sampled. This process is known as cluster sampling.

One more important cluster sampling method is to define the objective population as the particular livestock within a region differentiated by a well-defined topographical boundaries. Then an aerial sampling method is used where the region is divided into different sub units, with all the animals in a single unit being defined as a single cluster. The main advantage of this procedure over the others is

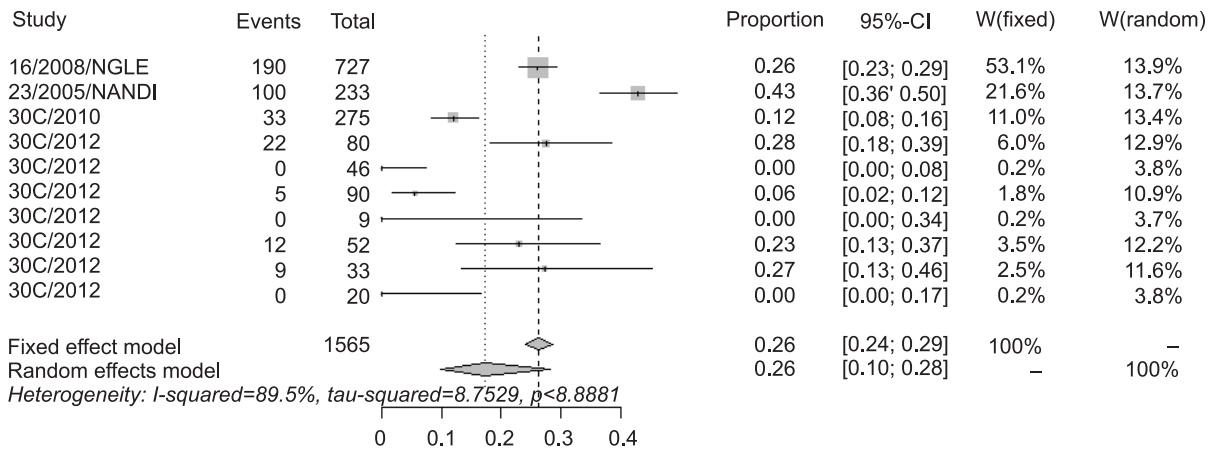


Fig. 6. Forest plot for Maharashtra goat population studies generated through meta-analysis for bluetongue disease.

that the investigator is confident about totally how many areal units are exactly present, and this in turn helps him to construct a sampling frame easily.

Purposive sampling: This method of sampling has no appropriate usage in the epidemiological studies involving livestock population.

Role of meta-analysis in livestock disease informatics

Meta-analysis can be defined as a systematic review of literature which is supported by statistical methods where the goal is to cluster and contrast the findings from various related studies. As science is a cumulative process, one can often find hundreds of studies addressing the same basic questions (Wolfgang Viechtbauer *et al.* 2010). Researchers are trying to cluster and synthesize the results of literature on those specified questions where they are increasingly conducting meta-analyses. In meta-analysis several models like fixed effect model, random effect models and mixed effect models are used to address the heterogeneity between studies (Jonathan *et al.* 2004).

The *Forest plot* and the *Funnel plot* are the two principal graphical methods used for meta-analysis where both are available in the most univariate meta-analytic situations (Tsairidou *et al.* 2014)

The forest plot in Fig. 6 has resulted from a meta-analysis and gives the disease prevalence for bluetongue virus amongst goat population in Maharashtra during the years 2005, 2008, 2010 and 2012 at 95% confidence interval and follows the Random effect model as the heterogeneity between studies is statistically significant.

A funnel plot is a visual tool for the investigation of the publication and any other bias in a meta-analysis study. They can be visualized as simple scatter plots with a horizontal axis of the estimated treatment effects from individual studies against a vertical axis of study size measurement. It is based on the accuracy in the estimation of the increase in the underlying treatment effect as there is an increase in the sample size of component studies. Hence, when there is no bias observed, results from the small studies will widely scatter at the bottom of the plot, showing narrowing

spread among the larger studies (Dominik D Alexander *et al.* 2009).

The funnel plot in Fig. 7 given below has resulted from a meta-analysis and gives the publication bias for the research carried on the prevalence of bluetongue virus amongst goat population in Maharashtra during the years 2005, 2008, 2010 and 2012.

Dendrograms in disease evolution

Rooted and unrooted phylogenetic dendrograms provide the information on the evolution of different infectious diseases. Now-a-days, various softwares viz., DNA Star, Lasergene, MEGA and Phylip etc. help in computing dendrograms that group/clusters/clades the nucleotide sequences obtained from different infectious agents. Pig farming is an important animal husbandry activity in North East region of India which is affected mainly by viral disease called classical swine fever (CSF) which causes 100% mortality. Movement and evolution of CSF virus helps in

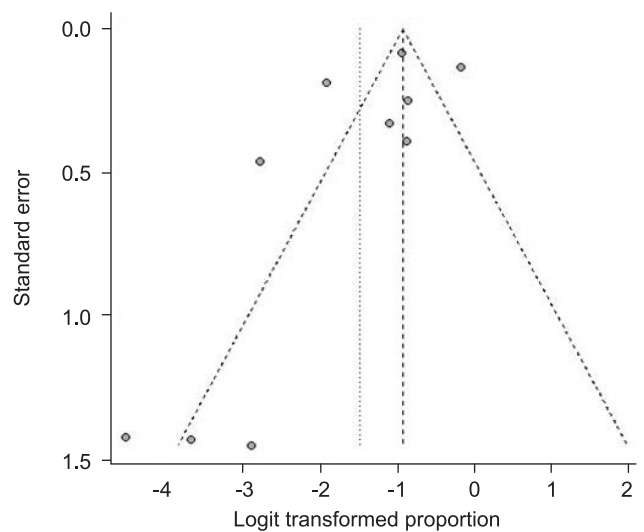


Fig. 7. Funnel plot showing the publication bias for Maharashtra goat population studies generated through meta-analysis for bluetongue disease.



Fig. 8. Phylogenetic tree computed using Phylip programme showing the clusters of CSFV into different subgroups. The tree was obtained using the sequences of 5'UTR genomic region of CSFV.

understanding the epidemiology of the disease (Patil *et al.* 2010, 2012; Shivaraj *et al.* 2013a, 2013b, 2013c 2013d, 2014, 2015; Choori *et al.* 2014, 2015). The phylogenetic tree shown in Fig. 8 was from Classical swine fever virus evolution.

One of the key problems in developing surveillance and control measures for livestock diseases in India is the limited understanding of epidemiology at aggregate level. Thus, more consideration is warranted for application of advanced statistical approach or models to assess their ability to understand epidemiology and predict factors responsible for disease occurrence or spread. The effective use of GIS and RS to identify the environmental features allows the

determination of risk factors and their areas of risk. This may permit more rational allocation of resources for disease control at best cost benefit ratio.

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