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Evaluate Risk Analysis of Measurement Uncertainty (MU) of Different Methods Applied for Veterinary Vaccines Evaluation

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ABSTRACT

Veterinary Serum and Vaccine Research Institute (VSVRI) objected to producing highly efficient vaccines from reference or local isolates according to the international specifications for protecting animals and poultry against different diseases and preparing combined vaccines to save effort, time and money. VSVRI produces various types of vaccines such as live attenuated viral poultry, live attenuated viral animal vaccines, live attenuated Bacterial animal vaccines and Inactivated viral animal vaccines. These vaccines are subjected to quality assurance through seven methods with different techniques. Validity and measurement uncertainty for results were applied in the evaluation of results of the following: Titration of virus content using egg inoculation through Chorioallantoic Membrane (CAM), Intra-allantoic (IA) and Tissue Culture (TC). Determination of antibody titer using ELISA, HI and VNT techniques. Finally, enumeration of aerobic bacterial count for living attenuated Bacterial vaccine by culture technique. Homogeneity and stability results for all vaccines were accepted criteria according to TS/ ISO 22117. The reproducibility component of the TC technique was higher while the Bias was lower than other different routes of egg inoculation. In conclusion, the accuracy of TC technique is better than the egg inoculation technique which will reflect on the measurement of uncertainty. There is no significant change in the final measurement uncertainty of different routes of egg inoculation. In comparison, there is a variance between bias accuracy and reproducibility precision due to the equation of measurement of uncertainty depending on all processes performed in test accuracy and precession.

Keywords: Bias accuracy and reproducibility precision, Measurement uncertainty, Vaccine.

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INTRODUCTION

Demonstration of laboratory's competence to conduct testing achieved by third-party accreditation. However, accreditation is only one part of establishing data credibility. The first component of a valid measurement system is validated test methods. Validation is defined as confirmation by examination and the provision of objective evidence that the particular requirements for specific intended use are fulfilled (***ISO/IEC 17025, 2017***). Most requirements in the international and national standards are methods validation and require that laboratory-developed methods or methods adopted by the laboratory should be suitable for the intended use.

Client agreement (i.e., end users of the test results such as veterinarians, animal health programs, and owners) for the validated methods and their uses is a requirement too (***ISO/IEC 17025, 2017***) and the validated method must be conducted by qualified personnel with adequate resources. This article discusses considerations and recommendations for development, validation and evaluation of risk analysis of Measurement Uncertainty (MU) for different methods applied for veterinary vaccines evaluation**.** These recommendations are based on nationally and internationally accepted standards and guidelines and the author's experience in assessing method development in the ISO/IEC 17025 environment.

Precision and accuracy are two independent measures for the performance of a diagnostic test. Precision refers to the closeness of an agreement among repeated measurements of the same sample and accuracy is how close or far of an agreement between the result of measurement and the value of the analyte measured (**Dybkaer, 1995) and (ISO/IEC GUIDE 99, 2007)**. It lacks worth if every measurement made has no association or quantitative statement of measurement errors. Quantification for boundaries of a measurement error is called measurement uncertainty (MU) **(NATA, 2009).** The OIE quality standard defines Measurement uncertainty as a parameter associated with the result of a measurement that characterizes the imprecision of the values that could reasonably be attributed to the analyte measured (**OIE, 2016)**.

Any analytical result is influenced by a complex of three major error groups: Random errors associated with the original sample matrix, the analytical (test) sample, the culture media, etc. Inherent systematic errors are associated with the analytical procedure. Modifying the systematic errors due to a particular laboratory's environment and equipment and individual analysts' personal traits in the test procedure (**Appendix J- STWG, and ISO3534-2, 2006).**The measurement of uncertainty [MU] is an essential component of a quality system for veterinary diagnostic laboratories which can provide quantitative estimates of the level of confidence that a laboratory has the analytical precision of test results; MU can be regarded as a combined measure of precision and Bias, where precision measures the ability to repeat the result each time. Bias measures the ability to produce an accurate result from the same tested sample (**NPAAG, 2009).**

Uncertainty and validation study should be done with skilled, qualified staff and good infrastructure with a quality assurance system to provide adequate confidence in the validation study results. There are many possible sources for the measurement of uncertainty and validation. Measurement equipment and test methods are not the only sources of measurement but also the person performing the test, data analysis, the environment and a host of other factors **Guidance G104 (2014).**

Measurement uncertainties may be classified as either random or systematic depending on how the measurement was obtained (an instrument could cause a random uncertainty in one situation and systematic uncertainty in another) **(Pelz *et al.*, 2021)**. Random uncertainties are statistical fluctuations (in either direction) in the measured data. The random uncertainties may be masked by the precision or accuracy of the measurement device. Random uncertainties can be evaluated through statistical analysis and can be reduced by averaging over a large number of observations. On the other hand, systematic uncertainties are reproducible inaccuracies and could be caused by an artifact in the measuring instrument or a flaw in the experimental design; it is not uncommon to see the term "systematic error." These uncertainties may be difficult to detect and cannot be analyzed statistically. If a systematic uncertainty or error is identified when calibrating against a standard, applying a correction or correction factor to compensate (**Bradley and Drechsler, 2014).**

Measurement of uncertainty reflects accuracy and perfect for the reliability of result to unable decision maker for accepts or refuse the goods. So, risk analysis related to the measurement uncertainty estimation is critical in evaluating vaccine production.This article aims to evaluate the Risk analysis of Measurement Uncertainty (MU) of seven methods applied for veterinary vaccine evaluation according to ISO/IEC 17025.

MATERIALS AND METHODS

Vaccine Samples

A total of 120 samples are used for each method from four different produced live vaccine batches and 120 samples from serum samples against three inactivated vaccines after three weeks post-vaccination.

- Two types of vaccines representing egg-adapted vaccines prepared on chorioallantoic membrane (CAM) as Fowl Pox vaccine (Fowl Pox Virus) and intra allantoic route as Newcastle vaccine (ND) (LaSota) **(OIE, 2021).**
- One type of Tissue culture-adapted vaccine is Sheep Pox **(OIE, 2021).**
- Serum samples against Rift Vally Fever were tested by VNT **(OIE, 2021).**
- Serum samples against IBD were tested by ELISA (**OIE, 2016**).
- Serum samples against Avian Influenza H_9N_2 AI tested by HI test (**OIE, 2016**).
- Brucella vaccine was evaluated by total colony count (**CFR, 2021).**

VSVRI provides all vaccines and serum samples, and titration values were determined for each type according to the standard method reference mentioned above under repeatability and reproducibility conditions.

Quality assurance

Quality assurance is important for verification of the accuracy and precision in the formation obtained from analysis ensuring that the data obtained from the analysis are suitable for use in decision making, ensuring the correctness of data and ensuring proper functioning to decrease maintaining equipment failure (***ISO/IEC 17025,* 2017).**

Performance of equipment

All equipment used was kept in clean and good working condition before use. The equipment was monitored according to working conditions and the accuracy demanded the results **(ISO/FDIS 7218, 2007).** All equipment and monitoring devices used were calibrated to traceable national standards.

Environmental monitoring

The temperature was checked periodically. The microbiological quality of air was checked before the beginning of the study. The microbiological quality of the surface was checked before analysis of the samples by using swap technique (acceptable limit <20 CFU/plate). The environmental control offers reasonable assurance that the environment is not a source of contamination of samples under testing **(*ISO/FDIS 7218,* 2007).**

Media and reagent performance

The media used in this study were tested before use to validate their efficacy and performance, including the measure of productivity and selectivity, to ensure that the media were suitable for each purpose **(*ISO/TS 11133-1,* 2014).**

Negative analytical controls

To ensure freedom from certain viral and bacterial contamination to be used in the evaluation of vaccines, Media were controlled by sterility tests to ensure that the analytical medium was not contaminated with the analyte and checked during preparation as the schedule for quality control **(ISO/IEC 17025, 2017).**

Criteria of validation

MU in veterinary diagnostic testing is not entirely reproducible; no exact value can be associated with the measured analyte. So, the result is most accurately expressed as an estimate together with an associated level of imprecision. It is not an alternative to test validation but is rightly considered a component of the validation process. Because there is MU associated with serological and different diagnostic measurements, the framework against which MU must be applied given by the standard against which the laboratory is accredited. To achieve accreditation, the ISO/IEC 17025:2017 standard requires the competence of testing and calibration laboratories (**Eurochem Guide, 1998).**

Statistical Methods and Measurement of Uncertainty

The measurement uncertainty was confirmed by two techniques first one**,** Nordtest TR 537 which is based on Reproducibility and Bias's component obtained from the control chart **(ISO 8258, 2005)**, and the second ISO19036 which is based on technical uncertainty depend on a standard deviation of reproducibility, Matrix uncertainty and Distributional uncertainties.The measurement uncertainty depends on the follower tools for start evaluation reproducibility, competent and Bias competent which are based on mean, standard deviation, true value, bias uncertainty, Reference value uncertainty, $(Bais)^2$, bias uncertainty, relative standard deviation (RSD) and RSD% measured according to ***ISO/TS 11133-2,* (2014)** rules for out of control to be checked according to ***ISO 8258,* (2005) and Excentral Version 2.1, (2008).**

Nordtest TR 537 is also A tool for estimating the measurement uncertainty (MU) according to Nordtest technical report 537: Handbook for calculating measurement uncertainty in environmental laboratories and validated excel sheet produced by Qual Lab. German**) (*Nordtest TR 569,* 2006** and ***Nordtest TR 537,* 2004)** in which the MU is calculated from estimating reproducibility and method Bias by using control charts, Proficiency tests and CRMs as follows:

1- Bias = (main - true value) x 100 / true value
2- RSD% = (STD / mean) x 100
3- Recovery = (mean / true value) x 100
4- Ref value uncertainty =100 x (error / 1.96 / true value)
5- Bias component= (sqrt $((Bias)^2$+ (bias uncertainty) ^{2}+ (Ref value uncertainty) ^{2})) ^{2}
6- Measurement Uncertainty =2 x sqrt $(Sr)^2$ + (bias component) ^{2}
7- error= sqrt of ((uncertainty of micropipette) ^{2} + (uncertainty of balance) ^{2}+ (uncertainty of reference Strain) ^{2})

Homogeneity of test material

Five randomly selected test materials were analyzed for each analyte and calculated according to (**Fearn and Thompson, 2001)**

Stability of test material

Samples to be used for testing should be stable, at least for the period from preparation (by VSVRI) to the date of the study or the end of the period allowed (***ISO/IEC17043,* 2010).** The minimum period for stability testing should be the time between the preparation of the materials and the specified date or time period of analysis. The stability was done according to (***ISO 22117,* 2010).**

RESULTS

The study was conducted on the assay of virus content in four types of vaccines; two of them are egg-adapted vaccines, one for Brucella vaccine and the last one is a tissue culture-adapted vaccine. A total of 120 samples were used to determine the validity of methods and measurement uncertainty. Each type of vaccine was examined for 12 weeks with different person and batch materials (SPF eggs, traceable batch of strain, cell culture and batch of media).

The stability for different batches of each type of vaccine was performed according to (**ISO 22117, 2010).** All validation data were subjected to Statistical analysis by MINITAB to determine Normal distribution at a confidence level of 95% (Figs 1 to 6).

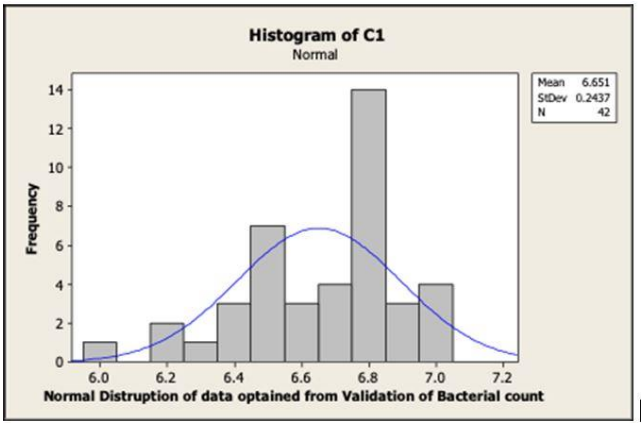

Fig.1: Normal distribution at confidence level 95% for Bacterial count.

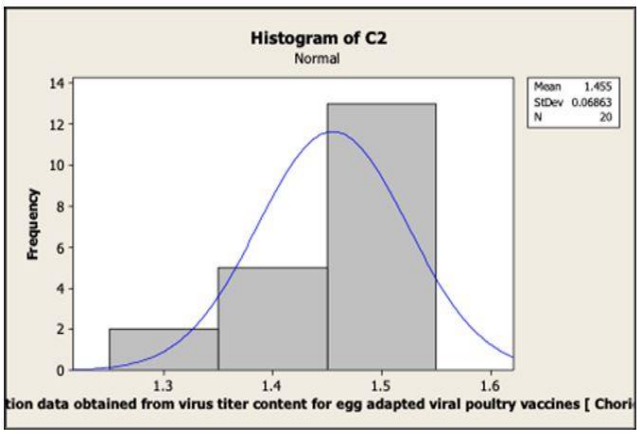

Fig.2: Normal distribution at confidence level 95% for virus titer content by chorioallantoic route.

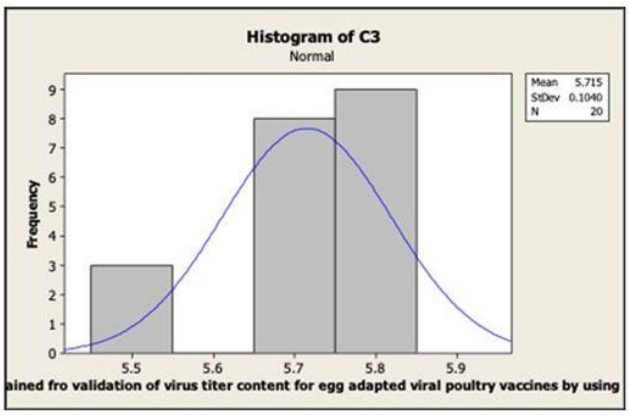

Fig.3: Normal distribution at confidence level 95% for virus titre content by Intrallantoic route.

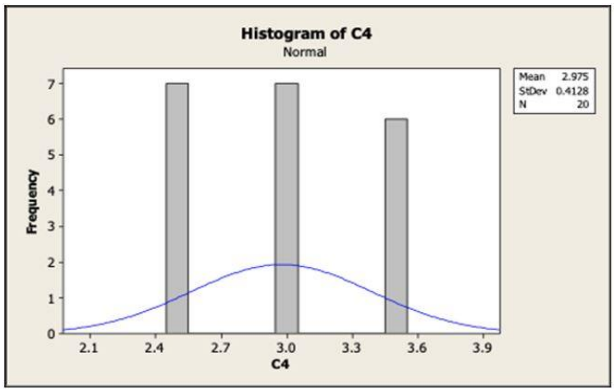

Fig. 4: Normal distribution at confidence level 95% for Virus titer by using tissue culture (TC).

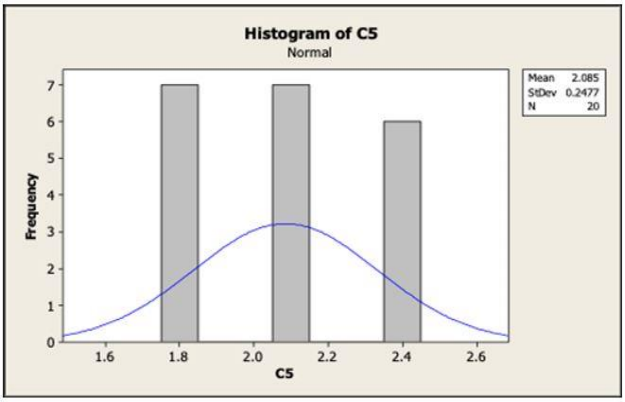

Fig.5: Normal distribution at confidence level 95% for Anti-body titer) by using Virus Neutralization Test (VNT).

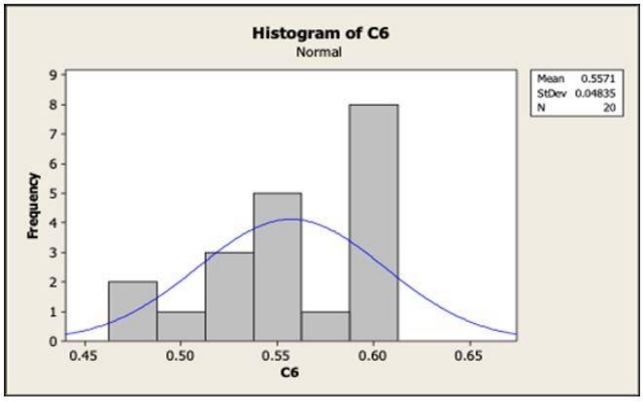

Fig.6: Normal distribution at confidence level 95% for Anti-body titer Serum samples) (IBD) by ELISA.

Table 1: Statistical Evaluation of Results for different 7 methods.

Statistical analysis for Validation data	Enumeration of aerobic bacterial count	Virus titre by IA	Virus titre (CAM)	Virus titre by (TC)	Anti-body titre by ELISA	Anti-body titre by HI test	Anti-body titre by using (VNT)
Reference Value	6.63	5.7	1.5	3.0	0.55	6.25	2.1
Mean	6.65	5.7	1.455	2.975	0.56	6.25	2.08
SD	0.21	0.1	0.07	0.41	0.05	0.05	0.25
N	20.0	20	20	20	20	20	20
True value	6.50	5.7	1.5	3.0	0.55	6.25	2.1
Repeatability	0.59	0.29	0.19	1.17	0.14	1.2	0.70
RSD%	2.59	0.02	4.72	13.88	0.09	0.07	11.88
Recovery %	0.43	100.3	97	99.2	99.48	1.26	99.3
Error	2.59	0.15	0.15	0.29	0.1	0.6	0.21
Bias %	0.04	4.78	-3.0	-0.83	1.82	0.0	-0.71
(bias uncertainty)	0.10	0.41	1.05	3.10	1.93	1.59	2.66
Ref value uncertainty	0.036	5.10	5.10	4.93	9.28	4.89	5.10
Bias component	1.23	7.00	6.50	5.88	9.6	5.15	5.79
(Reproducibility component)^2 = (RSD%)^2	0.02	3.31	22.25	192.52	0.008	50.53	141.11
(Bias component)^2	1.51	7.00	42.25	34.60	92.16	26.42	33.60

Table 2: Measurement uncertainty for each kind of vaccine was determined **(Nordtest TR 569, 2006)** and the results are represented in table 2 and figures from 7 to 10.

	Enumeration of aerobic bacterial count in live attenuated vaccine	Virus titer by (Intra-allantoic rout) (IA)	Virus titer Chorioallantoic Membrane] (CAM)	Antibody titer Serum samples) (IBD) by ELISA	Antibody titer (AI) (H9N2) by HI test	Antibody titer) by using Virus Neutralization Test (VNT)	Virus titer by using tissue culture (TC)
Measurement Uncertainty (Expanded Uncertainty) %	35	12.34	16.47	19.33	10.32	26.44	30.16

Table 3: Results of the validation study with the measurement uncertainty.

Methods	Technique	Results	Result in measurement uncertainty
Enumeration of Aerobic Bacterial count in live attenuated vaccine	Bacterial Count	6.65 Log_{10} cfu/ dose	6.65 Log_{10} cfu/ dose ± 2.33
virus titer content for egg-adapted viral poultry vaccines [Chorioallantoic Membrane]	virus titer content By CAM	1.46 log $_{10}$ EID_{50} /dose	1.46 ± 0.24
virus titer content for egg-adapted viral poultry vaccines by using egg inoculation (Intra-allantoic route)	virus titer content By allantoic rout	5.72 log $_{10}$ EID_{50} /dose	5.72 ± 0.71
Virus Titer in live attenuated vaccine Using Tissue Culture	virus titer content By TC	2.98 log $_{10}$ $TCID_{50}$ /dose	2.98 ± 0.9
Estimate antibody titer of inactivated large animal vaccines by using Virus Neutralization Test (VNT)	Estimate Antibody By VNT	2.09 log2	2.09 ± 0.55
Estimate antibody titer Serum samples against (Infectious Bursal Disease) by ELISA	Estimate Antibody By ELISA	0.56 OD	0.56 ± 0.11
Antibody titer (AI) (H9N2) by HI test	Estimate Antibody By HI	6.25 log2	6.25 ± 0.65

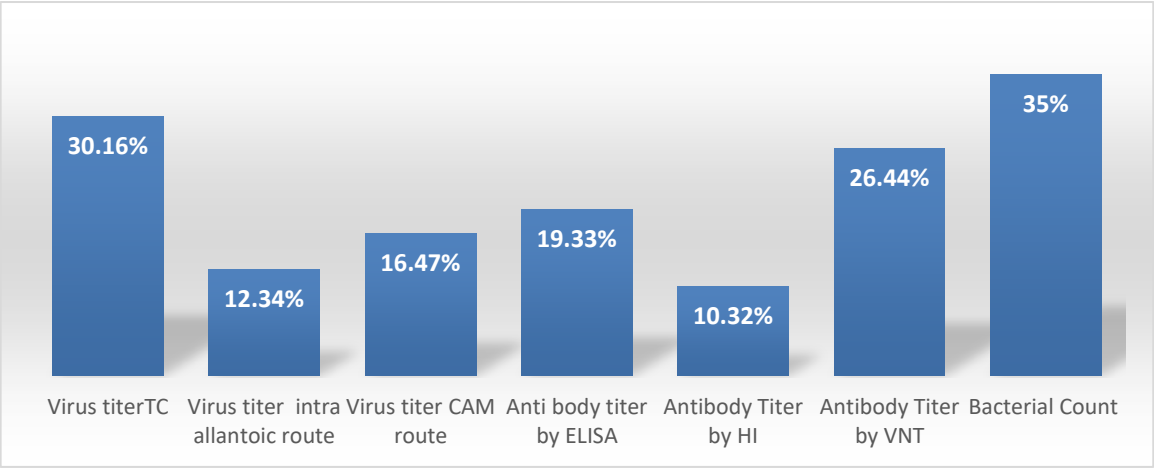

Fig.7: Measurement uncertainty for different 7 methods applied in QCL.

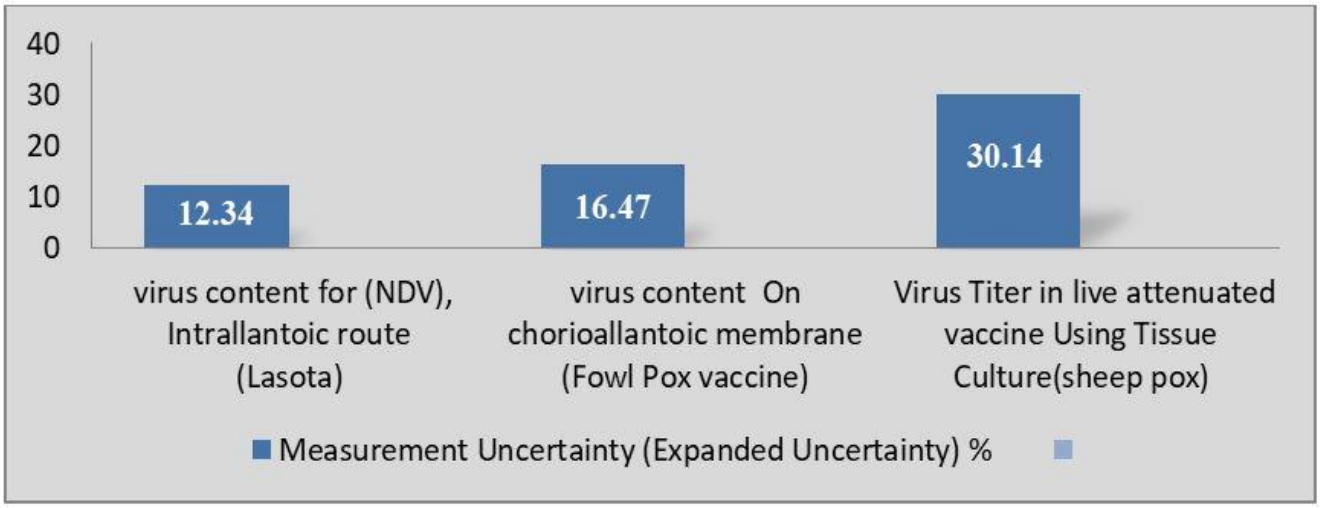

Fig. 8: Comparison of Measurement Uncertainty of Determination of Virus Titer by Different Techniques.

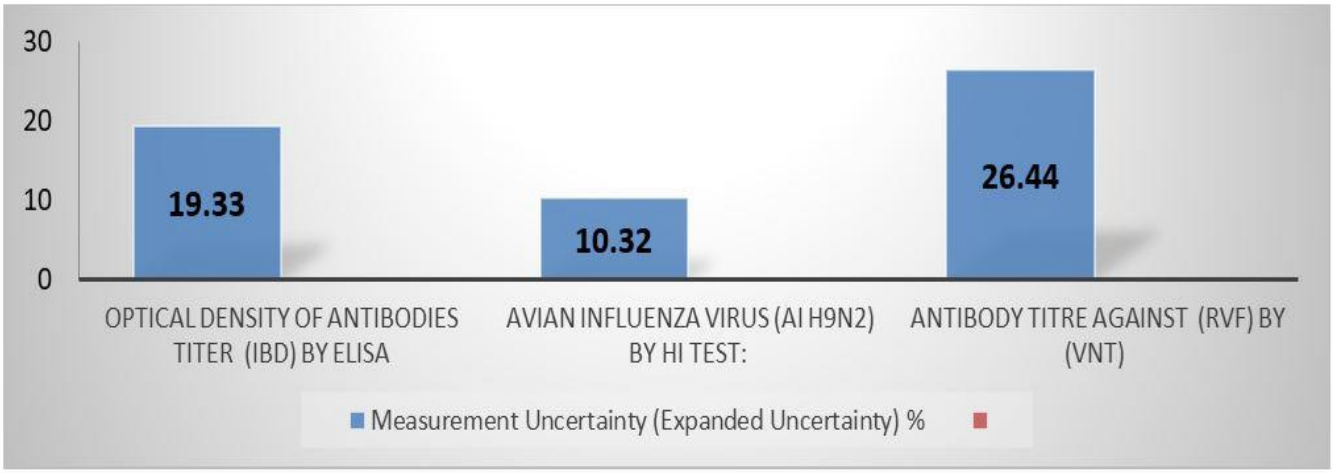

Fig.9: Comparative between Measurement Uncertainty of Determination of Antibody Titer by Different Technique.

Table 4: Statistical analysis of component of measurement uncertainty for different technique.

Method of analysis	Reproducibility component %	Bias component %	Uncertainty %
Virus Titer by TC	13.75	6.19	30.16
Virus Titer IA route	3.9	4.78	12.34
Virus Titer CAM route	4.72	6.75	16.47
Antibody Titer ELISA	0.56	9.65	19.33
Antibody Titer HI	0.44	5.14	10.32
Antibody Titer VNT	11.87	5.87	26.44
Bacterial Count	6.8	7.4	35.0

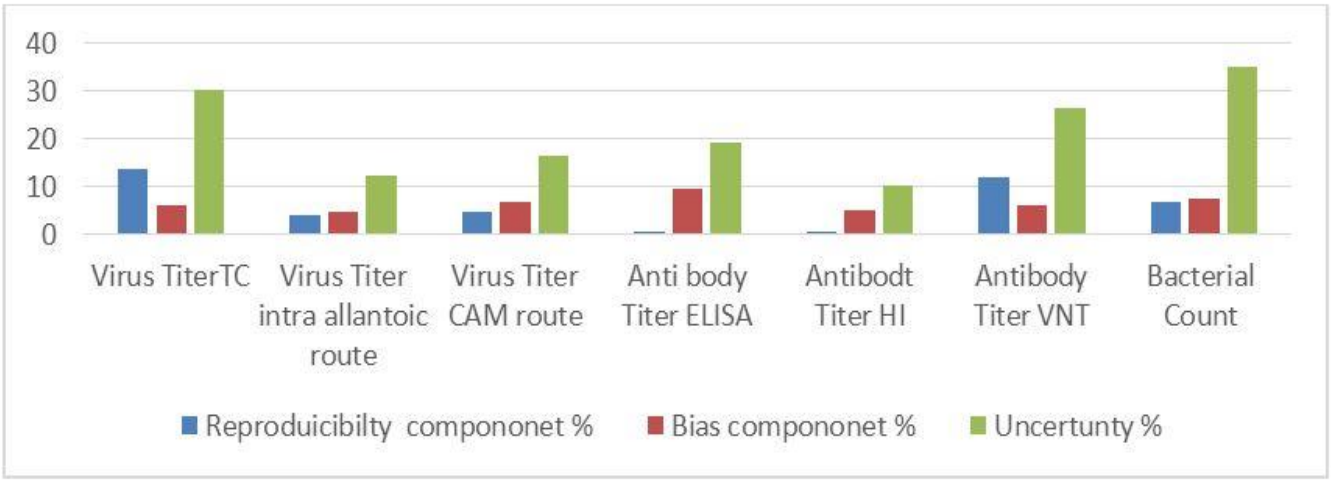

Fig.10: Uncertainty and its Component for Different Methods.

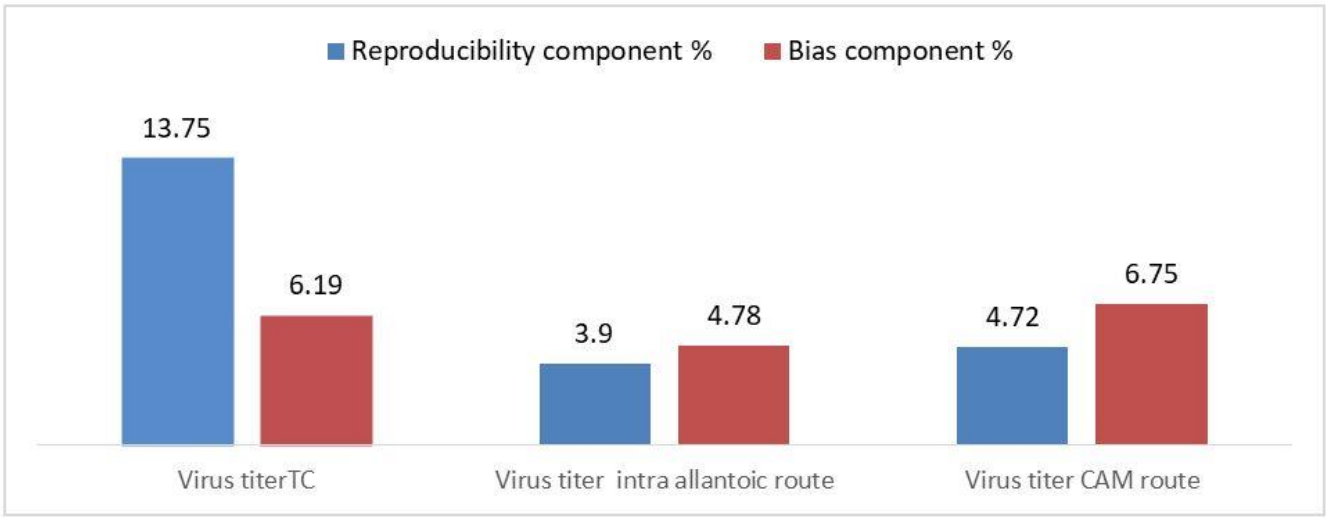

Fig. 11: Reproducibility and Bias component for virus titration by different technique.

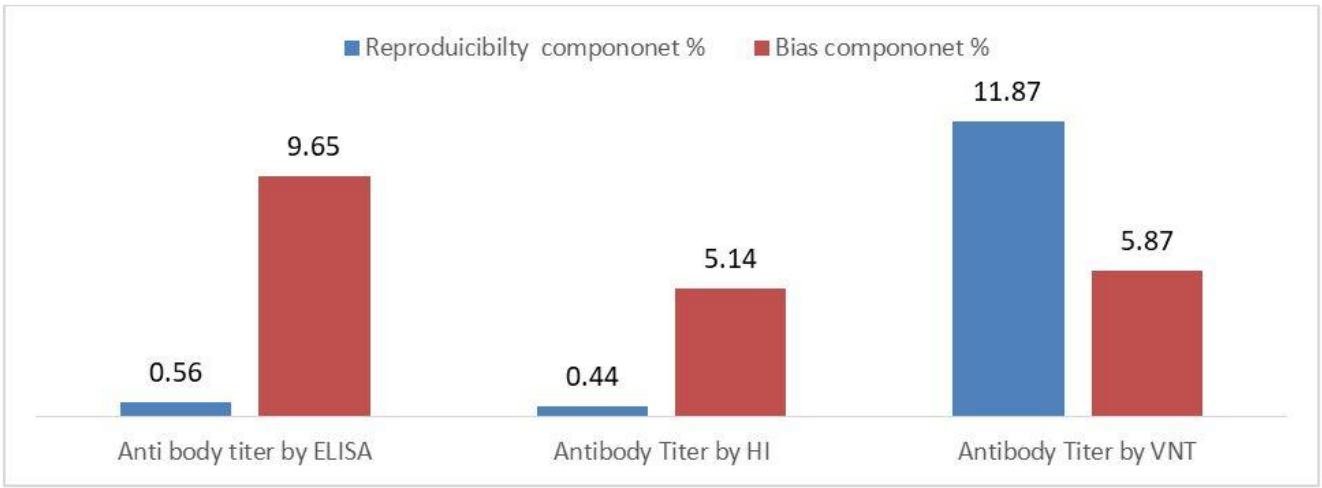

Fig.12: Reproducibility and Bias component for antibody titer by different technique.

DISCUSSION

Measurement uncertainty is estimated by two main approaches Nordtest TR 569(2006). Chemical and physical testing laboratories follow the 'components' or 'bottom-up' approach tend to follow this approach because potential sources of uncertainty are usually readily identifiable. All sources of uncertainty are individually identified in an exceedingly 'fish-bone' diagram, and their magnitudes will be estimated and combined. There are published attempts that medical testing laboratories to use this approach in validation. For instance, in serological tests, the uncertainties for time, temperature, volume, reading (Optical Density), operator and reagent batch were identified to estimate the general MU of the strategy **(Dimech *et al.*, 2006).**

The advantage of this approach is that the foremost sources of uncertainty are clearly identified and weighted individually, which indicates that reagent batch-to-batch, lab-to-lab and operator variation contributed significantly to the entire variation. Whereas reading, volume and temperature contributed to a lesser extent. The disadvantage is that it's time-consuming because it requires a posh statistical model and repeated measurements of every component. On the other hand, the 'control sample' or 'top-down' approach is suitable for medical and veterinary assays which may monitor whole-of-procedure performance and directly estimate the combined MU of the test procedure. Upper and lower limits to approve or reject MU will depend upon the aim of the test. If the MU goal isn't met, it will be necessary to analyze the procedure to spot and modify uncertainty sources using the bottom-up approach. This approach's advantage is the availability of repeatability data in diagnostic testing laboratories and straightforward calculations. The disadvantage is that the result's a world MU for the complete procedure and fails to differentiate between individual contributing components.

Validated methods consistent with (**ISO/TS34SC9W03/16140, 2017)** provide information about precision, for instance, repeatability, reproducibility, accuracy, analytical, diagnostic sensitivity and specificity within established limits. Therefore, MU is a vital aspect of test validation but cannot replace it. Currently, MU is employed for test methods that produce quantitative results. This includes tests, where numeric results are calculated and expressed as positive or negative at a cutoff value. Suitable statistical measures for precise MU are mean values plus/minus 2 standard deviations (95% confidence level CI), relative variance (RSD) or coefficient to variation (CV) (**ISO 3534-1, 2006)**.

Pre- or post-analytical errors such as (sample suitability, collection, transport and transcription or reporting errors. Biological error as animal breed, sex, age, co-infection with other agents, pregnancy and immunity should be excluded when applying MU to the analytical procedure **(Dimech *et al.*, 2006).** The results shown in Figures 1.1 to 6.6 indicate that all validation data subject to Statistical analysis by MINITAB were Normal disruptions at a confidence level of 95% which reflects that the tools applied to determine and estimate measurement uncertainty were suitable and accurate.

The measurement uncertainty for seven different methods is represented in Figure No (7). In contrast, measurement uncertainty % for 3 other techniques for virus titre determination were illustrated in Figure (8), indicating that the route of inoculation effect measurement uncertainty and accuracy of results at Intrallantoic route the MU was 12.34 % while at chorioallantoic membrane was 16.47%. The virus titre using tissue culture was 30.14 %. This variance may be due to dilution errors **(Corry, 1982).**

Otherwise, figure No. (9) represent the measurement uncertainty for determining antibody titre using ELISA, HI and VNT were 19.33 %, 10.32 % and 26.44 %, respectively. At the same time, the measurement uncertainty for the bacterial count was 35.0 %. All results reflect that the different techniques among and between methods affect the measurement uncertainty, as discussed in detail by (**Janet *et al.*, 2007).**

The results are shown in Fig.10, describe the relationship of measurement uncertainty and its component for different methods applied in the study. The results shown in Figure (11) describe the relationship between reproducibility and Bias components for Virus titration by Different Techniques. The first impression: the reproducibility component of TC technique was higher (13.75) while the allantoic and CAM routes were 3.9 and 4.72, respectively. On the other hand, the Bias component % for TC, allantoic route and CAM route were 6.19, 4.78 & 6.78, respectively. So the test accuracy by allantoic route was better than different routes of egg inoculation and TC technique. The results are shown in figure No. (12) Describe the relationship of reproducibility and Bias components for antibody titer by a different technique. The first impression: the reproducibility component of the Antibody Titer VNT technique was higher (11.87) while at Antibody titer ELISA and Antibody Titer HI were 0.56 and 0.44, respectively. While the Bias component % for Antibody titer ELISA, Antibody Titer HI and Antibody Titer VNT were 9.65, 5.14 & 5.87, respectively. So the test

accuracy by Antibody Titer HI was better than different techniques. Accuracy measures alone cannot evaluate performance estimation (**Bruno et al., 2005)** expressed that bias and accuracy measures should be combined to give an overall performance measure.

The result is shown in figure No. (11 & 12) describe the variance between bias and reproducibility components in different methods. The bias components for Virus titre TC, Virus titer intra allantoic route, Virus titre CAM route, Antibody titer ELISA, Antibody Titer HI, Antibody Titer VNT & Bacterial Count were 6.19%. , 4.78 % , 6.75 % , 9.65 % , 5.14 % , 5.87 % ,and 7.4 % respectively, while the reproducibility were 13.75 %, 3.9 % , 4.72 % , 0.56 % , 0.44 % , 11.87% and 6.8 % respectively. The results indicated that the accuracy of the method represented by Bias is low and precision is very high, which is reflected by the reproducibility component due to the precision of staff and tools applied in the test performance.

Quality-oriented laboratories are always interested in monitoring the performance of their diagnostic tests for continual improvement. Internal quality controls over a range of expected results have become part of daily quality control and quality assurance operations of accredited facilities **(Manghani, 2011).** Results provide relevant information about different aspects of repeatability, e.g., intra- and inter-assay variation, intra- and inter-operator variation, intra- and inter-batch variation and inform about the level of robustness of a test procedure. The level of variation of a test result becomes increasingly important the closer the test value is to the cutoff value used to designate a test result as positive or negative **(OIE, 2009)**.

On the other hand, they normally have little doubt about test results on the extreme ends of the measurement scale and whether reference standards or calibrated controls against reference standards are used. Sub-Committee on Animal Health Laboratory Standards tends to call these results 'strong positive' or 'strong negative.' Defining a range of inconclusive, intermediate, suspicious, borderline, grey zone or equivocal test values falling between the positive and negative cutoffs is considered good laboratory practice **(Greiner *et al.*, 1995** and **WHO**, **2016)**.

In this study, the MU provides diagnostic test results and gives an estimate of the range of values extended around the cutoff. Once this range has been established, the laboratory needs to develop a risk assessment for follow-up samples that fall in the MU range. We can decrease this risk by retesting the same or a second sample and depending on the test's purpose and performance characteristics, in particular precision and accuracy. Results from internal quality controls can be easily applied to estimate MU using a top-down approach with a minimum of additional testing and fulfill the requirements of ISO 17025.

CONCLUSION

Measurement uncertainty is considered as one of the risk factors that affect in case of the final results on the border of accepted criteria the final results; that's why the quality control laboratory required more study to reduce the factors which affect the component of measurement reproducibility and Bias component for among different method and between technique. As well as the variance between Bias [accuracy] and reproducibility [precision] due to the equation of measurement of uncertainty depending on all processes performed in test accuracy and precession.

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Conflict of interest

The researchers acknowledge that there is no conflict of interest regarding the research idea and tools, actual, potential and financial, directly or indirectly.

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