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Original Research Article

Comparison of the Sensitivity of Sterility Tests Based on the Analysis of 2x2 Contingency Tables

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Abstract: The work is devoted to statistical methods for determining the comparative sensitivity of sterility analyzers with a binary scale: 1/0, +/-. The paper considers both traditional statistical test methods namely the direct binomial test, the McNemar test, and the new, highly sensitive Yefimov Method, and Pearson-Yefimov statistical test. First, the comparative effectiveness of statistical methods for assessing the sensitivity of testers is demonstrated on a specially developed model system (the Test Bench), and then on real experimental data. The data were obtained during the validation of a new tester and a new method for analyzing samples for sterility. The new method is compared with the old one, the certified method. The sensitivity of both new and old methods (testers) was already determined earlier by a direct non-statistical method, which allowed us to compare the results of the two approaches. The factors influencing the efficiency of statistical tests are revealed and described.

Keywords: Paired dichotomous data, 2×2 contingency table, asymptotic significance (p-value), Binomial Test; Yefimov method for p-value, Yefimov Binomial test method; Pearson-Yefimov test method; Validation procedure for a new Rapid Microbiological Method.

ABBREVIATIONS
PDF – Probability density function
PMF – Probability mass function
CDF - Cumulative distribution function
AK - Adenylate kinase
ATP – Adenosine triphosphate
CFU – Colony forming units
LOD – Limit of detection

INTRODUCTION

In our previous work (Yefimov S, 2022), we described in detail a procedure for constructing a model system to compare dichotomous data statistical methods. In this work, we will briefly consider the model system, and supplement the collection of statistical test methods with the new Pearson-Yefimov test. We will compare the effectiveness of the methods and move on to the practical application of statistical tests for determining the statistically significant difference between the sterility tests, the sensitivity of which was previously determined by us not by statistical, but by direct approach (Yefimov SV, 2022). The sterility tests were done during the validation procedure. During the validation procedure for a new rapid microbiological method, two sets of dichotomous data are collected (USP 1223, 2008), the first data set is the data obtained by the reference method, and the second data set is the data obtained by the new method. The data are organized in 2x2 contingency tables (Felsenstein J, 2010), and the asymptotic significance (p-value) is calculated using either the Binomial test, McNemar's test, or Fisher's exact probabilistic test (Felsenstein J, 2010; Abdi H, 2007). Based on the analysis of p-values, it is concluded which method is more sensitive. However, if the currently accepted procedures for validating a rapid microbiological method are followed, it is very common for a p-value >0.05, which indicates statistical equivalence of the methods tested, although according to other, independent assessments the

sensitivity of the methods differs significantly. In this work, we will identify the reasons that affect the effectiveness of the analysis, modify the statistical method of analyzing 2x2 contingency tables, and give examples of the successful application of the modified method.

MATERIALS AND METHODS

Chemicals and instruments

Incubator 32.5°C ± 2°C; Celsis® Advance II; Celsis® Ampiscreen Reagent Kits; Vacuum manifold; Biological Safety Cabinet; Eppendorf BioPur pipette tips; PALL micro funnels – GN6 membrane 0.45 microns; Refrigerator; Freezer; Eppendorf Centrifuge 5415D; Eppendorf Centrifuge Tubes 1.5 mL; Bio balls (Biomerieux); Fluid Thioglycollate Medium (FTM); Tryptic Soy Broth (TSB); The microbiological procedure is described in detail (Yefimov SV, 2022). For sample preparation, we used Bioballs (Biomerieux) microorganism standards (Bioball (Biomerieux), 2022). PC HP Windows10, Free software "LibreOffice" version 6.0.0.3. The formulas are written in Excel notation for ease of use and reproduction of the results.

Experiment Design

The Test Bench for determining the relative sensitivity of binary testers includes the following components: 1. Three populations of normally distributed test objects, which can be molecular or colloidal solutions and suspensions, and populations of objects with recorded properties such as electric / magnetic field strength, electromagnetic radiation, noise, smell, weight, and any others. For definiteness and ease of perception, three hypothetical sand populations (light, medium, and heavy) are considered here, normally distributed over the weight of particles $N(\mu, \sigma^2)$. 2. In this case, hypothetical binary scales with different preset sensitivity (limit of detection) act as testers. 3. According to the results of hypothetical testing (weighing) on competing testers (scales), 2x2 contingency tables are built according to a certain algorithm. 4. The 2x2 tables are analyzed by various statistical tests such as the direct Binomial test, McNemar test, and others. The test results are compared, and the most sensitive statistical test method is determined. Attention is drawn to the factors influencing the determination of the mutual sensitivity of the testers, primarily to the differentiating and levering effects.

The Test Bench

Let us assume that have three grades of sand (A, B, C). Let us assume that the grains of sand of each variety have a normal mass distribution (N(0.5.1), N(2.1), N(4.1)) (Figure 1). Let us assume that we have two scales. The scale shows a positive result (or 1) if the weight exceeds the limit of detection (LOD), otherwise, the result is (0). Suppose we weigh randomly selected grains of sand from three populations (A, B, and C) on the control (1) and then on the test (2) scales. The results of the weighing of grains of sand are recorded in a 2x2 contingency table (Table 1).

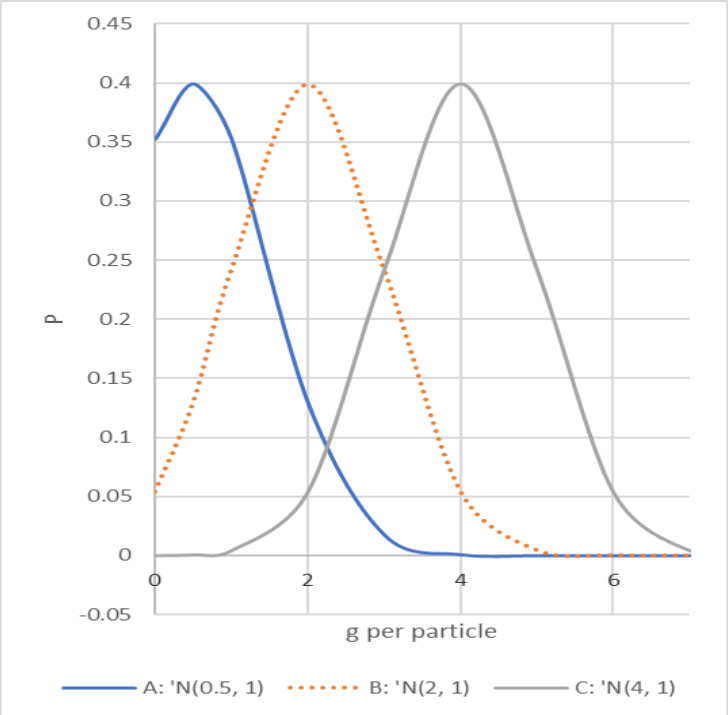

Figure 1: Probability density functions of the three populations of sand (A, B, C)

Table 1: 2x2 Contingency table

	Tester1 (+)	Tester 1 (-)	
Tester 2 (+)	a	b	a+b
Tester 2 (-)	c	d	c+d
	a+c	b+d	N=a+b+c+d

To populate the 2x2 contingency table based on the results of a hypothetical sand weighing, first, a 2x2 Probability Table is created (Table 2.) based on the population parameters N(μ, σ^2) and the tester sensitivities (LOD) we have chosen. The probabilities that the control balance -1 and balance -2 react to the weight (p1+, p2+) and do not react to the weight (p1-, p2-) when weighing a randomly selected grain of sand are calculated by the formulas which are written in Microsoft Excel notation:

1. **p2+= 1-NORMDIST(LOD2, μ, σ, 1)**
2. **p2-= NORMDIST(LOD2, μ, σ, 1) - NORMDIST(0, μ, σ, 1)**
3. **p1+= 1-NORMDIST(LOD1, μ, σ, 1)**
4. **p1-= NORMDIST(LOD1, μ, σ, 1) - NORMDIST(0, μ, σ, 1)**

Cells 2x2 of the Probability Tables are calculated by the formulas (*):

(*) a=(p2+)*(p1+); b= (p2+)*(p1-); c= (p2-)*(p1+); d= (p2-)*(p1-)

The probability (**P**) that the control scale responds to the weight of a grain of sand from the corresponding population is calculated by the formula:

(3a) P=p1+=1-NORMDIST(LOD1, μ, σ, 1).

Having done the necessary calculations, we get Table 2. To calculate contingency tables (Table 3) using the Probability Tables, each cell of the Probability Table is multiplied by a constant factor **Q** and the result is rounded up to an integer value. Thus, each contingency table we have built has 4 parameters: N(μ, σ^2), LOD1, LOD2, and Q.

Evaluation of the sensitivity of a tester according to the Contingency table

The resulting tables (Table 3) will be analyzed using two traditional statistical tests (direct Binomial test and McNemar test) and two highly sensitive tests (Efimov method and Pearson-Efimov test). The Efimov Method uses the differentiating effect of the low density of the test population (light sand) and uses the probability value (**P**) in the CDF formula of the binomial distribution (Yefimov S, 2022). We calculated the probability (**P**) using formula (3a), but now we can estimate this probability only based on contingency tables using formula (5):

(5). P=(a+c)/(a+b+c+d). If 2x2 contingency tables are built based on normally distributed populations, then the value calculated by the formula (5) is close to the theoretical one (formula 3a).

Analysis of 2x2 contingency tables

Binomial test

In statistics, the Binomial test is an exact test of the statistical significance of deviations from a theoretically expected distribution of observations into two categories. A binomial test can be used, where b (Table 1) is compared to a binomial distribution (Figure 2A): $PMF(b,n,P)= C^n_b P^b(1-P)^{n-b}$ with size parameter n = b + c, integer variable b from 0 to n, and **P** = 0.5. The Null Hypothesis ($\mathbf{H_o}$) is $P_b=P_c= 0.5$. The goal is to calculate the p-value (or asymptotic significance) using a 2x2 contingency table and Binomial distribution. A p-value ≤ 0.05 indicates a statistically significant difference, and strong evidence against the null hypothesis, so the null hypothesis should be rejected (Abdi H, 2007).

In the present work, we use the right-tailed p-value (formula 6), because we assume that the second tester is more sensitive, and b≥c in the 2x2 contingency table:

(6) p-value(b, n, P)= 1-BINOMDIST(b-1,n,P,1)

We set right-tailed p-value =1 if n=0, and right-tailed p-value = 1 if b=0 to escape error marks.

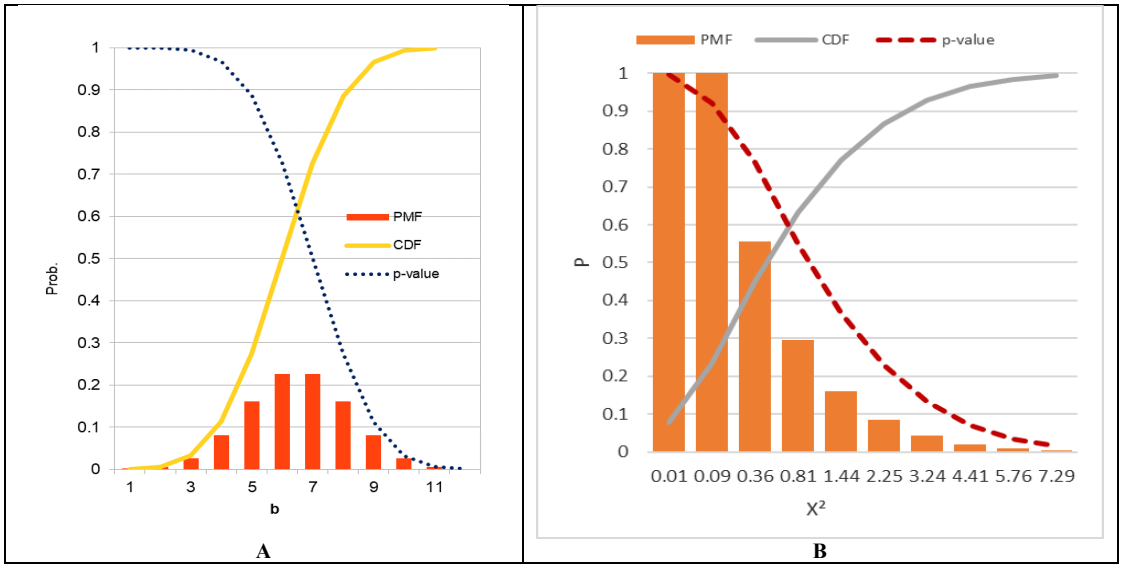

Figure 2 A, B: PMF, CDF, and right-tailed p-value. A - Binomial distribution PMF=BINOMDIST(b, n, p, 0) where n=11, p=0.5; B- χ^2-distribution PMF = CHISQ.DIST(χ^2,0)

Modification of the Exact Binomial test (Yefimov Binomial test)

For proper evaluation of testers, it is necessary to refuse to fix the probability (P=0.5). As we saw in the three types of sand example, this probability can vary. In this case, we consider the Null Hypothesis **(H_0)** must be written as **Pb=Pc=P** against the one-sided alternative hypothesis **(H1) Pb>Pc**. The value of **P** in each case is different, it depends on the tested population and can be assessed from the data of the contingency table, by formula (5). Recall that the probability **P** is the probability of obtaining a positive test result by a control tester of a randomly selected object from a given population. The Yefimov Method (Yefimov S, 2022) uses the Differentiating Effect of a low-density population (Figure 3) and the probability value (**P**) in the binomial distribution CDF formula. For normally distributed data, the value of **P**= (a + c) / N indicates which population we are dealing with, differentiating, integrating, or intermediate (Figure 3, Tables 2 and 3). However, if the distribution is far from normal, the value of **P** indicates something different. The differential effect. For light sand (A), in all cases, when the given sensitivity of balance -2 exceeds the sensitivity of the balance -1 (LOD2<LOD1), the p-value calculated by the Yefimov Method is less than the significance level, which indicates against the Null hypothesis and favor to Alternative hypothesis N1. In other words, the analysis confirms the different sensitivity of the scales. Medium. When testing balances using medium sand (B), the advantage of the more sensitive tester is revealed only when the sensitivity ratio LOD2/LOD1=1/2 or less. The leveling effect occurs if we are testing the heavy sand (C). In this case, the test does not reveal the statistical difference between the scales (Figure 3).

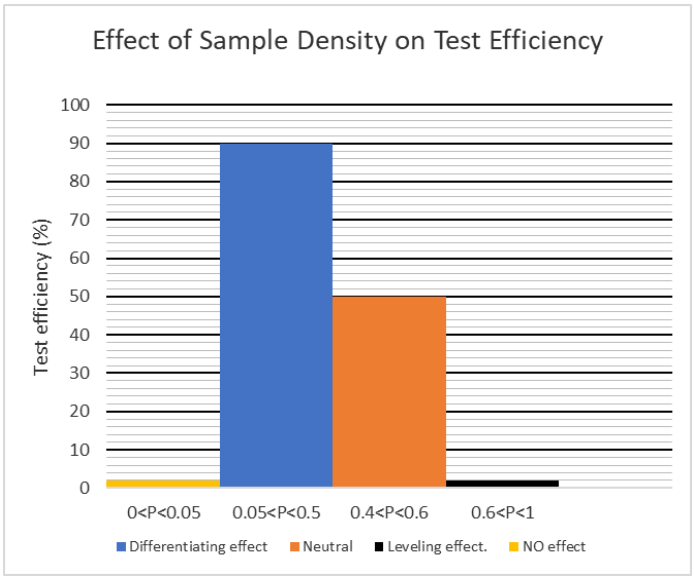

Figure 3: Diagram illustrating the advantage of low density (concentration) samples in statistical analysis of 2x2 contingency tables. As an Efficiency, the percentage of LOD2 from LOD1 was taken, at which the differences are statistically significant. The probability of success (P) for the control tester may be used as a criterion for choosing the population with the differential effect. The data presented are rough estimates or qualitative data

McNemar's χ^2-test

In statistics, McNemar's test is a statistical test used on paired data. It is applied to 2×2 contingency tables (Table 1) with a dichotomous trait, with matched pairs of subjects (McNemar Test Definition, 2022). The null hypothesis (H_o) is $p_b=p_c$. The McNemar's test statistics is: $\chi^2 = (b-c)^2/(b+c)$, $(b+c)\neq 0$, Using the Chi-squared distribution (Figure 2B), we calculate the p-value as follow: p-value = 1-CHISQ.DIST(χ^2,1).

Chi-squared test (Pearson-Yefimov χ^2-test)

Inspired by the idea of Karl Pearson (Pearson K, 1900), we will compose the test statistics as follows: $\chi^2 = (O1-E1)^2/E1 + (O2-E2)^2/E2$. Where O1 is tester -2 positive results, E1 is control (tester-1) positive results, O2 is tester- 2 negative results, E2 is control (tester- 1) negative results. Using the 2x2 contingency tables denotation the Pearson-Yefimov test statistics formula may be rewritten as follow: $\chi^2 = (b-c)^2/(a+c) + (c-b)^2/(b+d) = (b-c)^2N/(a+c)/(b+d)$ where $(a+c)\neq 0$, $(b+d)\neq 0$. The null hypothesis (H_o) is: $p_b=p_c$. Using the Chi-squared distribution (Figure 2B), we calculate the p-value as follow: p-value = 1-CHISQ.DIST(χ^2,1). If a+c=0, then p-value is set to zero.

The result of calculating one-sided right-tailed asymptotic significance for the LOD2 is equal to 1.5, and for three populations of sand light (A, N(0.5,1)), medium (B, N(2, 1)), and heavy (C, N(4, 1)) are presented in Table 4. The bold numbers are p-values<0.05.

Table 2: Example of 2x2 Probability Tables. These 3 tables are based on three probability density distributions for two detection limits of conditional testers. LOD1=2, LOD2=1.5

A, N(0.5, 1)		B, N(2, 1)		C, N(4, 1)	
0.0334	0.3123276	0.4666	0.44537	0.97702	0.02271
0.01279	0.119598	0.02203	0.02103	0.0002	4.6E-06
P=0.0668072		P=0.5		P=0.97725	
p2+ =0.5		p2+ =0.93319		p2+ =0.99977	
p2- =0.1914625		p2- =0.04406		p2- =0.0002	
p1+ =0.0668072		p1+ =0.5		p1+ =0.97725	
p1- =0.6246553		p1- =0.47725		p1- =0.02272	

Table 3: Example of 2x2 Contingency tables, derived from Table 2. Q=30, LOD1=2, LOD2=1.5. Probability (P) was calculated by the formula (5)

A (light)		B (medium)		C (dense)	
0	3	10	10	29	1
1	10	4	4	0	0
P=0.071		P=0.5		P=0.97	

Table 4: The result of calculating the p-value for three contingency tables (Table 3.) by four statistical methods

Yefimov Binomial test.		
A	B	C
p-value=0.00	p-value=0.09	p-value=0.97
Pearson-Yefimov. χ^2- test		
A	B	C
p-value=0.038	**p-value=0.023**	p-value=0.31
Exact Binomial test.		
A	B	C
p-value=0.31	p-value=0.09	p-value=0.50
McNemar. χ^2-test		
A	B	C
p-value=0.32	p-value=0.11	p-value=0.32

Similarly, we calculated Tables 2, 3, and 4 for LOD2: 1.8; 1.0; and 0.5 at LOD1=2, as well as a negative control. The negative control (LOD2=LOD1=2), as expected, gives the p-value>0.05 by all four statistical methods. As a result, we got the number of the efficiency of statistical methods Figure 4.

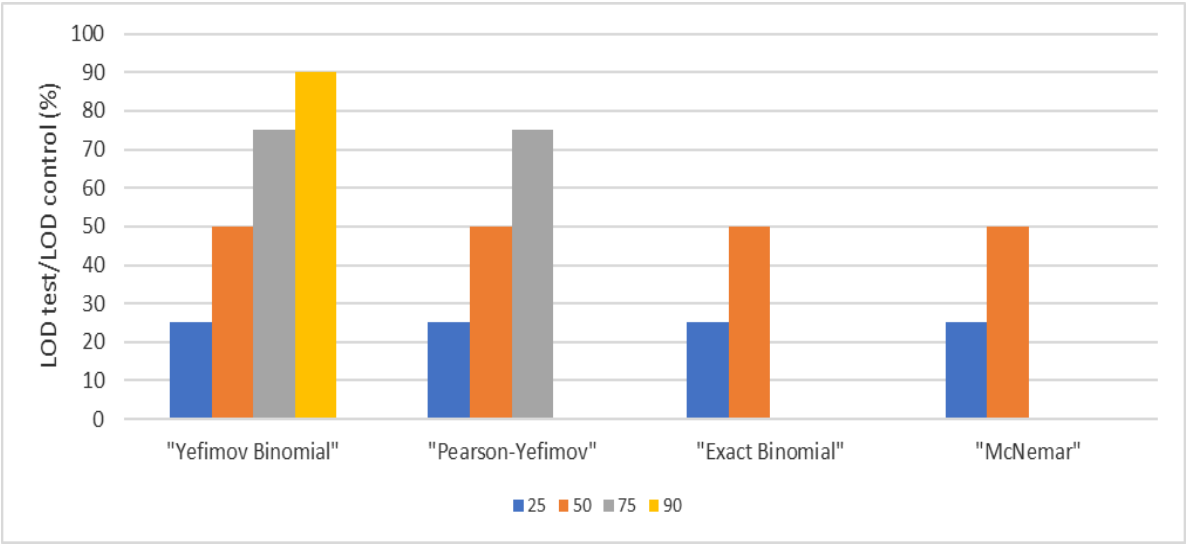

Figure 4: Comparison of the Efficiency of four statistical methods. The maximum ratio of LOD2/LOD1 (%) at which the statistical test method gives the p-value<0.05 is designated as the measure of the Efficiency of the statistical test method

This completes the description and verification of the Test Bench. The Test Bench itself is a finished product. It can be used to model the testing of various objects, both normally distributed and otherwise. With its help, we can evaluate and compare the performance of statistical test methods. Summarizing all the above, we emphasize the most important functions of the Test Bench: 1) Modeling 2x2 contingency tables. To do this, the distribution parameters of the tested object are set (mean (μ), and standard deviation (σ)), the sensitivities of two binary testers (LOD1, LOD2) are set, and the value of **P** is determined. 2) For the given ratio 0<LOD2/LOD1 <1 determines which of the statistical test methods makes the difference statistically significant (p-value<0.05). Now we can proceed to the analysis of a real experimental data.

RESULTS AND DISCUSSION

The equivalence or nonequivalence of two test methods that detect microbiological contamination was evaluated by comparing the rate of positive and negative results obtained from identical samples. The methods were: the Rapid Adenylate Kinase-amplified ATP bioluminescence method (AK) (The Celsis Advance II™ system, 2000), and ATP bioluminescent method without AK (ATP) (Pallchek™ Rapid Microbiology System, 2021). Also, we used 2 conventional, growth-based methods, the Plate count method (Plate), and the growth of microbial cells in liquid media with visual detection of turbidity (Vis.) (Sandle T, 2014). The sensitivity of the methods was determined in our previous work with the use nonstatistical, direct method (Yefimov SV, 2022). The number of sensitivities of the methods is as follows: AK> Pl>ATP, it corresponds to the number of LODs: 0.05< 1 < 500 (CFU/100μL). The limit of detection of the visual method (Vis.) was not determined, we attribute to it the same LOD as the Plate method (LOD=1) since both methods are growth-based. The difference in LODs of the methods is very large and we expect statistical methods to confirm this (Table 5). In the first group, cells at concentrations of 10, 1, and 0.1 CFU in an appropriate growth media were incubated for 4 days. After incubation, the suspensions were tested by two competitive methods (Table 5 rows 1-8). In the second group, aqueous cell suspensions of 1, 0.5, and 0.1 CFU were tested immediately after the preparation of the suspensions (Table 5 rows 9-13). Row 14 shows the simulation results of cell suspension testing (1 CFU/100μL) by the Plate method and by the AK method (σ=1, μ=1, LOD1=1, LOD2=0.1). Row 15 shows the simulation results of cell suspension testing (1 CFU/100μL) by the ATP method and the AK method (σ=1, μ=1, LOD1=1000, LOD2=0.1). The abbreviations: Asp., Cl., Ps., Bac., St., Ca., and Prop. Ac. are mean Aspergillus brasiliensis, Clostridium sporogenes, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Propionibacterium acnes (slow-growing cells population), respectively.

Table 5: Statistical analysis of 2x2 contingency tables. a, b, c, and d are the cells of a 2x2 table. (*) - cells concentration is 1.0 (CFU/100μL)

Test#	Cells	Tester2/ Tester1	a	b	c	d	p-value Yefimov Binomial	p-value Exact Binomial	p-value Pearson-Yefimov	p-value McNemar	P
1	Cl.	AK/ATP	9	0	0	6	1.000	1.000	1.000	1.000	0.600
2	Asp.	AK/Vis.	5	0	0	10	1.000	1.000	1.000	1.000	0.333
3	Asp.	AK/ATP	6	0	0	9	1.000	1.000	1.000	1.000	0.400
4	Bac.	AK/Vis.	8	0	0	7	1.000	1.000	1.000	1.000	0.533

Test#	Cells	Tester2/ Tester1	a	b	c	d	p-value Yefimov Binomial	p-value Exact Binomial	p-value Pearson-Yefimov	p-value McNemar	P
5	Ca.	AK/Vis.	4	0	0	11	1.000	1.000	1.000	1.000	0.267
6	St.	AK/Vis.	8	0	0	7	1.000	1.000	1.000	1.000	0.533
7	E.Coli	AK/Vis.	7	0	0	8	1.000	1.000	1.000	1.000	0.467
8	**Prop.Ac.**	AK/Vis.	0	5	0	10	**0.000**	**0.031**	**0.000**	**0.025**	0.010
9	Bac. *	AK/ATP	0	19	0	16	**0.000**	**0.000**	**0.000**	**0.000**	0.100
10	St. *	AK/ATP	0	20	0	14	**0.000**	**0.000**	**0.000**	**0.000**	0.100
11	E.Coli *	AK/ATP	0	15	0	15	**0.000**	**0.000**	**0.000**	**0.000**	0.100
12	Prop.Ac.*	AK/ATP	0	5	0	13	**0.000**	**0.031**	**0.000**	**0.025**	0.100
13	Prop.Ac.*	AK/Vis.	0	6	0	12	**0.000**	**0.016**	**0.000**	**0.014**	0.100
14	Model *	AK/Plate	12	8	0	0	**0.017**	**0.004**	**0.000**	**0.005**	0.600
15	Model *	AK/ATP	0	21	0	1	**0.000**	**0.000**	**0.000**	**0.000**	0.010

In the first group, except for row 8, there are no statistical differences. This fact confirms our previous conclusion about a 10^5 - 10^6-fold increase in the concentration of most cells during incubation in a nutrient medium (Yefimov SV, 2022). That is, here we are dealing with a pronounced leveling effect. The leveling effect (Rows 1-7) is also confirmed by the fact that for a slow-growing cell population the leveling effect is not expected, and the asymptotic significance <0.05 is established (Row 8). In the second group (Rows 9-13), the p-value <0.05 is established by all four methods, and this is consistent with our previous data, where it was shown that the difference in the sensitivity of the sterility tests (AK/ATP, AK/Vis.) is 20 times or more (Yefimov SV, 2022). Such a large difference warrants a p-value of <0.05 across all 4 statistical tests because even the less sensitive Binomial test and McNemar's test detect a 2-fold difference (Figure 4.). It should be noted that about half of the samples in the first and second groups were sterile (cells “d”), and this requires reflection. The simulation experiment (rows 14 and 15) gives the expected result for all four statistical tests. An important difference from real experiments is that there are no or almost no sterile samples (cells “d”). This is how it should be for a normally distributed population. In a real experiment, the number of sterile samples is large, and the distribution looks like a binary one. Out of N samples, m contains cells, and l is sterile (N=m+l). With such a distribution, one cannot rely on the value of P as a criterion for the differentiating effect.

The reason for the significant number of sterile samples lies in the work of the laboratory assistant in the Microbiological Room. Disinfection rules, constant microbiological monitoring, and administration requirements force the laboratory assistant to clean the work surface, tools, and hands with a disinfectant solution (isopropyl alcohol) more often and more than necessary. As a result, vapors and aerosol of the disinfectant are constantly concentrated around the working surface, which leads to the sterilization of a significant part of the samples.

Highly sensitive statistical methods the Yefimov Binomial test and the Pearson-Yefimov test, which have the efficiency of 90% and 75%, turned out to be too good for these sterility analyzers because their sensitivity difference is tens and hundreds of times.

For correct analysis, it is most important to use the Yefimov Method, the meaning of which is to select conditions: (LOD2≈M<LOD1, 0<P<0.5) (Yefimov S, 2022). In the first group (rows 1-7, Table 5), the value of M, in this case, this is the concentration of cells, is 10^5 - 10^6 CFU, as was shown previously (Yefimov SV, 2022), and such a concentration is much higher than the LOD of any of the testers so that the difference between them can be statistically revealed impossible.

CONCLUSION

The relative sensitivity of tests for sterility was determined by statistical methods of analysis of 2x2 contingency tables. Both traditional and new highly sensitive tests were used, namely the Efimov Binomial test and the Pearson-Yefimov test. The results of statistical testing were compared with the results of determining the sensitivity of the tests for sterility obtained earlier by direct methods (Yefimov SV, 2022). The results matched. The pairwise ratio of sensitivities is as follows: AK-method>ATP-method, AK-method>plate-method, AK-method>visual-method.

The most important condition for correct statistical analysis is the correct choice of cell concentration averages in the test population. Selection criteria are formulated in the Yefimov Method (Yefimov S, 2022).

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