PERFORMANCE OF THREE TECHNIQUES FOR THE SURVEILLANCE OF CONGENITAL MALFORMATIONS. A COMPUTER SIMULATION TEST.

G. BARBUJANI and E. CALZOLARI

INTRODUCTION

In the study of congenital malformations, surveillance is the analysis of frequencies, in order to distinguish random fluctuations of such frequencies from non-random trends, namely significant decreases or increases. In the latter case, surveillance systems should trigger an alarm, which should be followed by further epidemiological studies.

Several surveillance techniques have been proposed, and the present study will deal with the results of a computer test on them. An alarm situation was simulated, and the performances of three different surveillance techniques were checked in various experimental conditions.

MATERIALS AND METHODS : SURVEILLANCE TECHNIQUES.

A synthetic description of the rationale of the statistical techniques tested is in Table I.

TABLE I : Techniques for the surveillance of birth defects.

	RELEVANT QUANTITY	CONSTANCY OF TOTAL NUMBER OF BIRTHS
O/E RATIO	Malformation frequency in constant periods of time	not assumed
CUSUM	Malformation frequency in constant periods of time	assumed
SETS	Gap between two consecutive malformed babies	not assumed

In the OBSERVED/EXPECTED RATIO technique (BAILAR and EDERER, 1964), the alarm is given when the observed malformation frequency in a given period of time exceeds significantly its Poisson expectation. This is called a "not self-reinforcing method", since the increase in malformation frequency may be detected only within one of the lapses of time studied. Non-significant increases in successive lapses of time are not cumulated, and so the OBSERVED/EXPECTED RATIO technique is not able to show their overall effect.

On the other hand, the Cumulative Sum, or CUSUM technique (EWAM and KEMP, 1960; HILL et al., 1968) and the SETS technique (CHEN, 1978; CHEN et al., 1982) are "self-reinforcing methods", since non-significant increases in malformation frequencies, if occurring in successive intervals of time, may reinforce each other, yielding an alarm signal. The CUSUM gives an alarm when the difference between the observed malformation frequency and a constant reference value exceeds a certain threshold. The SETS technique gives an alarm when the gaps between two successive newborns carrying a specific defect are systematically shorter than a given threshold.

The SETS technique is applicable both to single hospitals and to the clumped data from a group of hospitals; here the single-community model will be tested. The CUSUM technique is applicable directly whenever the total number of births in the periods considered may be regarded as constant. This is often not true, and, in such cases, the CUSUM technique must be modified accordingly. In the present work, however, it is applied according to the simplest model.

MATERIALS AND METHODS : THE COMPUTER SIMULATION

In the present work, a sequence of random numbers from a rectangular distribution was generated (Monte Carlo methods; LEVIN 1969). Each computer-generated number was considered as representing either a healthy or a malformed newborn. In the first phase of the simulation, the malformation probability was held constant; in the second phase it was increased by a factor 2, or 3.5, or 5. The three surveillance techniques were applied along the two phases, thus allowing a control over false alarms (namely, alarm given in the first phase of the test, before the increase in malformation probability), over true alarms (alarms given in the second phase of the test, after the increase), and over missed alarms.

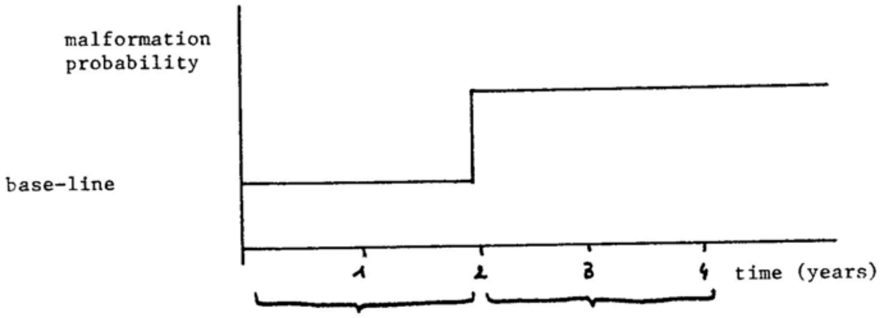
The simulated system was composed of three hospitals, with 300, 200 and 100 newborns per month, respectively. Every newborn was assigned by a particular algorithm to one of such hospitals. Four different baseline malformation probabilities were chosen : 1/435; 1/578; 1/660; 1/1193. These are the baseline malformation rates for four defects in Emilia-Romagna (Congenital cardiopathies; Down Syndrome; Multiple Malformations; and Cleft Palate/Lip, respectively). Six hundred births were simulated 24 times (months) using the baseline malformation rate. At the end of the 24th month, the malformation rate was increased, and 600 births were simulated for 24 more months.

The Cusum technique performed on the pooled births of the three centres, was computed at three-monthly intervals, i.e. after every 1800 births. The set technique was applied separately to the three centres and the first alarm in any centre, whether false or true, was registered as an alarm for the whole system. A "false negative" occurred only when none of the three centres had an alarm throughout the 48 month period.

For each malformation and each factor of increase, 40 runs of the simulation were carried out : thus, the experiment was repeated 480 times (40 times x 4 malformations x 3 factors of increase = 480).

A scheme of the possible outcomes, for each run of the simulation and each technique considered, is in figure 1. Since the alarm signal stopped the analysis of the sequence of newborns for that run, an increase in malformation frequency occurring after a false alarm could never be detected.

FIGURE 1. Possible outcomes for each iteration of the simulation test and each technique tested. TN = True Negative; TP = True Positive; FN = False Negative; FP = False Positive. (From BARBUJANI and CALZOLARI, 1984, modified).



	1st phase	2nd phase	test counted
FALSE ALARM	YES	-	once (FP)
TRUE ALARM	NO	YES	twice (TN, TP)
MISSING ALARM	NO	NO	twice (TN, TP)

RESULTS AND DISCUSSION

1. The results have been summarized in three decision matrices (Table 2). In the absence of increases in malformation rates (1st phase of each simulation) each technique was tested 480 times. The control in the presence of an increase in malformation rates was possible only for the runs in which a false alarm had not been issued. The high number of False Positives registered by the OBSERVED/EXPECTED RATIO technique is evident : they are 151, versus 22 for the CUSUM, and 44 for the SETS technique. On the other hand, no alarm was missed by the OBSERVED/EXPECTED RATIO technique, versus 14 for the CUSUM and 36 for the SETS technique. In most cases, such False Negatives occurred in the presence of 2-fold increase in malformation probability, and for the less common of the defects simulated (Cleft Palate/Lip).

2. Three indices (Table 3) of the effectiveness of diagnostic procedures, namely sensitivity, specificity and accuracy were used (MC NEIL AND ADELSTEIN, 1976). The sensitivity of the OBSERVED/EXPECTED RATIO is 100%, bur this is reached at the expense of a very low specificity. In other words, that technique appeared the most error-prone by giving a high number of false alarms. Therefore, the ratio of correct outcomes to all outcomes, accuracy, was about 80% for the OBSERVED/EXPECTED RATIO, while the CUSUM technique and the SETS technique are shown to be more accurate; the former appeared to be more accurate that the latter.

TABLE II : Decision matrices

	Increase present	Increase absent	Total	
Alarm given	329	151	480	
Alarm not given	0	329	329	
Total	329	480	809	O/E RATIO
Alarm given	444	22	466	
Alarm not given	14	458	472	
Total	458	480	938	CUSUM
Alarm given	400	44	444	
Alarm not given	36	436	472	
Total	436	480	916	SETS

3. The delays between the increases in malformation probability and the alarm signal were calculated (Table 4). The cases in which a false alarm had been given were neglected. The missing alarms were considered as having an arbitrary 27-month delay (3 months more than the maximum observable delay) in the computation of the averages. The alarm delays appeared to be correlated with the magnitude of the factor of increase applied. The good sensitivity of the OBSERVED/EXPECTED RATIO was confirmed, while the performances of the self-reinforcing methods were comparable. The CUSUM technique, however, gave, on the average, quicker correct outcomes than the SETS technique.

TABLE 3 : Sensitivity, specificity, accuracy of the three techniques.

	O/E	C	S	
Cardiopathies	1.000	1.000	0.970	Sensitivity = $\frac{TP}{TP+FN}$
Down syndrome	1.000	1.000	0.936	
Multiple malformations	1.000	0.975	0.901	
Cleft palate/lip	1.000	0.905	0.870	
Cardiopathies	0.758	0.900	0.842	Specificity = $\frac{TN}{TN+FP}$
Down syndrome	0.742	0.967	0.908	
Multiple malformations	0.658	0.983	0.925	
Cleft palate/lip	0.583	0.967	0.958	
Cardiopathies	0.863	0.947	0.901	Accuracy = $\frac{TP+TN}{TP+FP+TN+FN}$
Down syndrome	0.852	0.983	0.921	
Multiple malformations	0.794	0.979	0.913	
Cleft palate/lip	0.737	0.936	0.915	

TABLE 4 : MEAN ALARM DELAYS. False alarms disregarded, missing alarms considered as delay = 27 months. Totals are weighted averages.

	O/E	C	S
Increase = 2	8.3	12.8	14.8
Increase = 3.5	4.0	5.8	6.6
Increase = 5	3.2	4.3	4.4
Total	5.4	7.6	8.9

CONCLUSIONS

The OBSERVED/EXPECTED RATIO appeared to be very liable to false alarms. Although it permitted the correct detection of all alarm situations, it gave alarms also in a high fraction of the normal situations. As a consequence, its quickness is hardly useful. Therefore, it should not be considered an effective method for the surveillance of birth defects. Self-reinforcing methods appeared to be more reliable.

The performance of the CUSUM appeared slightly but constantly better than that of the SETS technique, especially in the presence of 2-fold increases in malformation probabilities. The CUSUM proved to be more sensitive to real increases, less liable to false alarms, and quicker in giving the alarm signals. A wider comparison of the two techniques is in progress, and confirms such observations (BARBUJANI and CALZOLARI, 1984, BARBUJANI, CECCHERINI and RUSSO, unpublished data on the performance of the Multicommunity model of the SETS technique).

At present the SETS technique does not seem likely to have any advantage over the Cusum technique, independent of the number of hospitals involved, the baseline malformation rate and the factor of increase in malformation rates.

REFERENCES

1. BAILAR, J.C. and EDERER, F.
Significance facturers for the ratio of a Poisson variable to its expectation.
Biometrics, 1964, 20 : 639-643.

2. BARBUJANI, G. and CALZOLARI, E.
Comparison of two statistical techniques for the surveillance of birth defects through a Monte Carlo simulation.
Statistics in Medicine, 1984, 3 : 239-247.

3. CHEN, R.
A surveillance system for congenital malformations.
J Amer Stat Assoc, 1978, 73 : 323-327.

4. CHEN, R., MANTEL, N., CONNELLY, R.R., ISACSON, P.
A monitoring system for chronic diseases.
Neth Inform Med, 1982, 21 : 86-90.

5. EWAN, W.D. and KEMP, K.W.
Sampling inspection of continuous processes with not autocorrelation between successive results.
Biometrika, 1960, 47 : 363-380.

6. HILL, G.B., SPICER, C.C. and WEATHERALL, J.A.C.
The computer surveillance of congenital malformations.
Br Med Bull, 1968, 24 : 215-218.

7. LEVIN, B.
Simulation of genetic systems.
In MORTON, N.E., Ed, Computer applications in genetics.
Hawaii University Press, Honolulu, 1969.

8. Mc NEIL, B.J. and ADELSTEIN, S.G.
Determining the value of diagnostic and screening tests.
J Nucl Med, 1976, 17 : 439-448.