Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1962, 27, 317-324

Prophylactic Effect of Antivaccinia Gamma-Globulin against Post-vaccinal Encephalitis *

Lt-Col. W. NANNING [1]

In the Netherlands, the frequency of encephalitis after smallpox vaccination is estimated to be 1 in 4000 primary vaccinations in adults and 1 in 50 000 revaccinations. Since immunity seems to reduce the frequency of this complication, it was thought that it might be possible to prevent post-vaccinal encephalitis by a combination of passive and active immunization, a basic immunity being obtainable without risk by the injection of antivaccinia gamma-globulin (AGG). This theory was tested in Dutch military recruits in a double-blind experiment. At the time of primary vaccination the recruits were given an injection in the other arm, either of 2 ml of 16% AGG (treated group) or of 2 ml of placebo solution (control group).

It appeared that administration of AGG had a prophylactic effect, since only 3 cases of post-vaccinal encephalitis occurred among the 53 630 recruits in the treated group, as compared with 13 among the 53 044 recruits in the control group. The difference of 10 is significant. The best estimate of the reduction in the frequency brought about by injection of 2 ml of 16% AGG is 77%; the lower limit of this reduction is 29%.

The administration of 2 ml of 16% AGG did not interfere with the development of active immunity.

Post-vaccinal encephalitis is a serious complication of smallpox vaccination; its frequency varies from one country to another. Since the first reports on Dutch cases were published (van Bouwdijk Bastiaanse, 1925a, 1925b), the frequency of this disease has been rather high in the Netherlands. It has been estimated at 1 in 4000 primary vaccinations among pre-school children. Revaccination involves much less risk, as no more than 1 in 50 000 revaccinations at various ages is followed by similar neurological complications (Terburgh, 1932; Nanning, 1955). Though the etiology of post-infectious disturbances of the central nervous system is not yet clear, it has been suggested that post-vaccinal encephalitis might be prevented by combining passive immunization with primary vaccination. Van Bouwdijk Bastiaanse (unpublished data, 1947) proposed that passive immunization be effected with antivaccinia serum derived from recently vaccinated individuals. His proposal was subsequently modified with regard to the exclusion of infectious agents present in human serum. At the request of the National Health Council, the Organization for Health Research TNO accepted the task of setting up a field trial with antivaccinia gamma-globulin (AGG) among recruits, in co-operation with the Medical Service of the Royal Netherlands Army and Royal Netherlands Air Force.

Gispen, Lansberg & Nanning (1956) studied in volunteers the effect of administration of AGG on primary smallpox vaccination, examining the local reaction and the development of neutralizing antibodies after injection of various doses of AGG 0-3 days before the scarification. They found that 1-6 ml of 16% AGG had no apparent effect on the development of pocks and antibodies.

Further investigations confirmed these conclusions. A group of persons who were successfully

* Report on a field trial carried out under the supervision of the Advisory Committee TNO on Post-vaccinal Encephalitis. The present members of this committee are: R. Gispen (Chairman); J. W. Tesch; B. J. W. Beunders; B. V. Bekker; R. van Dam; F. Dekking; H. S. Frenkel; M. F. Polak; A. B. F. A. Pondman; A. C. Ruys; W. G. Sillevis Smitt; J. D. Verlinde; J. Wester. The statistical adviser was E. F. Drion of the Statistics Department TNO. The histological examinations were performed by E. de Vries, neuropathologist at the Neurological Department, University of Utrecht. The investigation was carried out by the author in collaboration with members of the staff of the Medical Service of the Royal Netherlands Army and Royal Netherlands Air Force.

[1] Royal Netherlands Army Medical Corps.

TABLE 1

COMPARISON OF REVACCINATION REACTIONS IN PERSONS VACCINATED PRIMARILY WITH AND WITHOUT SIMULTANEOUS ADMINISTRATION OF 2 ml OF AGG

Interval between vaccination and revaccination (years)	Primary vaccination							
	With AGG				Without AGG			
	Number of individuals showing the following types of reaction after revaccination:				Number of individuals showing the following types of reaction after revaccination:			
	Immediate	Accelerated	Primary	Total	Immediate	Accelerated	Primary	Total
2-3	15	9	0	24	13	8	0	21
3-4	29	17	0	46	27	23	0	50
4	13	9	0	22	24	18	0	42
Total	57	35	0	92	64	49	0	113

given a primary vaccination with simultaneous administration of 2 ml of AGG were revaccinated at various intervals. In no case was the revaccination followed by a primary reaction. No substantial difference between the trial group and the control group was found (see Table 1).

Since no unfavourable effects were observed in these preliminary studies we felt justified in carrying out a field trial on a larger scale.

MATERIAL AND METHODS

Volunteers

In compliance with the legal requirements all Dutch recruits must be vaccinated or revaccinated against smallpox. Recruits therefore form a special population group, composed exclusively of men 19-25 years of age who have been selected for military service on the basis of a medical examination.

Before vaccination, a second selection is made, since the regulations require another medical examination, especially intended to exclude from vaccination those recruits for whom an increased risk of post-vaccinal encephalitis could be expected. A number of degenerative stigmata, a congenital predisposition to diseases of the central nervous system and a poor physical condition are considered as contra-indicatory. Individuals who have suffered from encephalitis are never accepted for vaccination. In the present investigation a few exemptions from vaccination were made on the above grounds. A recovered case of poliomyelitis or meningitis, however, was not rejected.

The recruits who were vaccinated were allocated at random to the trial group, which received AGG, or to the control group, which received a placebo.

Procedure

The following procedure was adopted for the vaccination. All vaccinators used the same technique throughout the investigation. A separate sterile vaccinostyle was used for each person vaccinated. Two parallel scarifications were made along the length of the arm, not more than 5 mm long and separated by at least 2 cm. The site of the vaccination was the area of the left deltoid muscle. The scarifications were covered with sterile gauze.

Immediately after the primary vaccination, 2 ml of AGG or placebo was injected into the right deltoid muscle, a separate sterile needle and syringe being used for each injection. The injection was then recorded.

The ampoules were distributed to the vaccinators in such a way that, among each group of 18 recruits, 9 received the AGG and 9 the placebo. The placebo was used in order to avoid psychological reactions to receiving no shot.

Donors and immune gamma-globulin

The donors of immune gamma-globulin were healthy volunteers from the Royal Netherlands Army and the Royal Netherlands Air Force. Blood was taken 4-6 weeks after a successful primary vaccination or 3-4 weeks after a revaccination resulting in a distinct pustule reaction. The blood from a single donor usually supplied sufficient AGG for the treatment of 2 or 3 persons. The AGG was prepared

by the Central Laboratory of the Blood Transfusion Service of the National Red Cross, Amsterdam, and was supplied in a concentration of 16% in 2-ml ampoules.

The placebo was prepared in the National Institute of Public Health, Utrecht, according to the following prescription:

Gelatin	20 g
Glucose	20 g
NaCl	5.5 g
Distilled water . . .	1000 ml

The pH of the solution was adjusted to between 6.8 and 7.0.

This gelatin-glucose solution was supplied in such a way that it could not be distinguished from the AGG by those who administered the injections.

Collection and evaluation of cases of post-vaccinal encephalitis

Recruits who showed very marked or alarming symptoms after vaccination, whether or not post-vaccinal encephalitis was suspected, were admitted to military or civilian hospitals, where they were examined by specialists who were ignorant of the kind of injection administered with the vaccine. Notification of these admissions to hospital was sent to the Department of Preventive Medicine of the Royal Netherlands Army Medical Corps.

The case-histories of patients with neurological symptoms after vaccination were sent to the Expert Committee on Post-vaccinal Encephalitis of the National Health Council. This committee studied the cases and classified them according to the following four categories.

I. Unequivocal cases of post-vaccinal encephalitis.

II. Somewhat doubtful, though almost certain, cases of post-vaccinal encephalitis.

III. Cases in which the arguments for and against a diagnosis of post-vaccinal encephalitis had equal weight.

IV. Cases in which little more was known than that the vaccination was followed by disease or death after such an interval that the possibility of post-vaccinal encephalitis could not entirely be excluded.

Statistical analysis was carried out by means of a sequential design.

RESULTS

The trial included a total of 106 674 individuals. Of these 53 630 belonged to the group that received AGG and 53 044 to the placebo group.[1] The investigation covered a period of 4½ years, ending May 1959.

The results were analysed with regard to the occurrence of febrile reactions and the frequency of post-vaccinal encephalitis and myocarditis.

Febrile reactions

For a period of 18 days after the primary vaccination the recruits were not allowed to leave their quarters. This permitted thorough observation. The relevant data were collected on lists, designed especially for the purpose, and included a temperature chart and a short case-history. Temperature was recorded at least once a day from the first day after the vaccination. According to regulations each vaccinated individual whose temperature rose above 37.5°C was admitted to an infirmary.

An investigation was undertaken to find out whether there were differences between the treated and control groups with regard both to the number of admissions and to the clinical symptoms.

Preliminary examination of about 500 lists showed a difference in the percentage of admissions. Therefore large groups of primarily vaccinated individuals from 111 units were examined for admission rates. The treated group, consisting of 4691 men, had 2750 (58.6%) admissions, while the placebo group, comprising 4629 men, showed 2931 (63.3%) admissions. The difference is 4.7% ($P<0.0001$). In 80 of the 111 units the percentage of admissions in the treated group was smaller. In 5 smaller units, which were not included in the above 111 units, the admission rate was the same for both groups. Since 80 is significantly higher than $\frac{1}{2}\times 111$ ($P<0.0001$), it could be concluded that the difference in the percentage of admissions was not caused by a small number of strongly deviating garrisons.

Other means were also used in an attempt to detect a possible effect from the AGG. The appearance of very marked or alarming symptoms, such as a vaccinated individual may show during vaccinia, was followed by admission to hospital. The indication for hospitalization was determined by the units'

[1] After the thirteenth case of post-vaccinal encephalitis the experiment was virtually finished. At that time 38 277 persons had been treated with AGG and 38 280 with placebo. After that time, owing to an error that occurred during the author's absence, some boxes containing 18 ampoules of AGG, which had been prepared in anticipation of the time when every recruit would be given AGG, were distributed along with the boxes containing 9 ampoules of AGG and 9 ampoules of placebo. The boxes were indistinguishable from one another and, consequently, the proportion of recruits receiving AGG was higher than 50%.

physicians. The data from 33 such cases were collected. Of these, 17 belonged to the placebo group and 16 to the treated group.

The hypothesis that AGG would exercise no unfavourable effect on the course of the vaccinia is not in contradiction with the above data.

Myocarditis

During the period of this investigation (4½ years) 11 cases of acute myocarditis occurred in the Army and Air Force. Of these patients, 8 had been subjected to primary smallpox vaccination within the three preceding weeks, but no such relation to smallpox vaccination was found in the other 3 cases. The average number of individuals who were primarily vaccinated each year was approximately one-quarter of the total strength. The frequency of myocarditis seems to be comparatively high in the 3-week period following primary smallpox vaccination.

It is very likely that primary smallpox vaccination predisposes to myocarditis. Administration of AGG does not seem to alter this very much, as 3 out of the 8 cases belonged to the treated group and 5 to the control group. However, the two deaths that occurred were in the control group.

Post-vaccinal encephalitis

In the course of the investigation a total of 51 cases was considered by the Expert Committee on Post-vaccinal Encephalitis of the National Health Council. Of these, 35 cases with various slight disturbances of short duration could not be diagnosed as encephalitis. These 35 cases were almost equally distributed between the two groups, 16 having received the AGG and 19 the placebo.

In the 16 remaining cases the diagnosis of post-vaccinal encephalitis could be accepted. A review of these cases is shown in Table 2. There was only one fatality in each group. The patient who died in the treated group had a complicating lung affection which played a part in the fatal course of the disease. At autopsy the cerebrum showed microglia

TABLE 2

CASES OF POST-VACCINAL ENCEPHALITIS

Case No.	Category	Diagnosis	Interval between scarification and onset (days)	Prophylactic treatment	Sequelae
1	I	Encephalitis	12	Placebo	Increased left-knee and Achilles reflexes
2	I	Myelitis	14	Placebo	None
3	I	Encephalitis	14	Placebo	None
4	II	Meningitis	?	AGG	None
5	I	Meningo-myelo-encephalitis	13	Placebo	None
6	I	Encephalitis	15	Placebo	None
7	I	Encephalitis	13	AGG	Death. Complicating broncho-pneumonia
8	I	Encephalitis	10	Placebo	Total loss of function of left auditory nerve
9	I	Encephalitis	13	Placebo	Irritability and changes in character
10	I	Encephalo-myelo-radiculitis	12	Placebo	None
11	I	Myelitis	13	Placebo	Transverse lesion. Complete disability
12	I	Myelitis	13	Placebo	None
13	I	Encephalitis	11	Placebo	None
14	I	Encephalitis	12	Placebo	Death. No autopsy
15	I	Encephalitis	?	AGG	None
16	II	Encephalitis	11	Placebo	None

reactions characteristic of post-vaccinal encephalitis (see de Vries, 1960) and vascular reactions such as are found in toxico-infectious encephalopathy. The latter reactions were considered to be the result of the many broncho-pneumonic foci which were found at autopsy.

The accepted cases of post-vaccinal encephalitis were classified for the greater part in category I. Only two cases fell into category II. Of the 16 patients, 3 had received the AGG and 13 the placebo (Table 2). The interval between scarification and onset of the complicating encephalitis varied from 11 to 15 days. The cases were distributed equally over the years of investigation and over the garrisons involved. In addition to the two fatal cases, there were more or less serious sequelae in four patients, all belonging to the placebo group. A transverse lesion resulting in complete disability was seen in one of them; another suffered a total loss of function of the left auditory nerve. In the third patient the terminal sequelae were slight changes of character and in the fourth increased left-knee and Achilles reflexes. The small number of cases does not permit a comparison of the two groups with regard to the gravity of the complicating encephalitis.

STATISTICAL DESIGN AND ANALYSIS

If a complication occurs with a frequency of about 1 in 4000 primary vaccinations in adults, the reduction brought about by prophylactic treatment of all vaccinees should be impressive if conclusions can be drawn within the limits imposed by the size of the groups and the period of investigation. In the event that administration of AGG proved to give appreciable protection against encephalitis, the earliest possible termination of the trial would be desirable. It was therefore decided to use a sequential design of analysis. In such a design the total number of observations is not determined beforehand, but depends on the results of the experiment.

The following specifications of the design were made in order to avoid missing a reduction of 66% or more in the frequency of the complication:

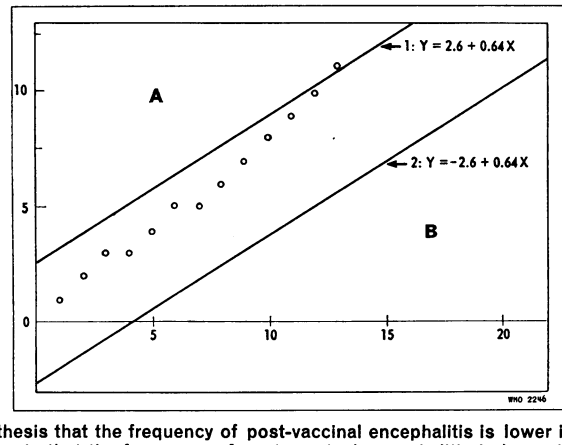
1. The probability that the conclusion that AGG gives no protection, when in fact it reduces by two-thirds the frequency of post-vaccinal encephalitis after primary vaccination, is incorrect is 0.05.

2. The probability that the conclusion that AGG gives some protection, when in fact it gives no protection at all, is incorrect is 0.05.

The recruits were vaccinated in groups of 18, of whom 9 received AGG and 9 placebo. The injections were performed in the order of the ampoules in the box, which had been filled in a random order. Therefore the allocation of the recruits to the placebo or the AGG was random. For the evaluation of the protective value of AGG, only those groups of 18 recruits in which just one recruit developed post-vaccinal encephalitis were considered. There were no groups in which more than one recruit developed post-vaccinal encephalitis. This could be expected, for even with a frequency of 1 in 4000 in both treated and untreated recruits, the probability that more than one case of encephalitis would occur in a group of 18 recruits is less than 10^{-5}.

For each post-vaccinal encephalitis patient a point was plotted on a graph (see accompanying figure);

ENCEPHALITIS CASES IN AGG GROUP *VERSUS* THOSE IN PLACEBO GROUP



A. Accept hypothesis that the frequency of post-vaccinal encephalitis is lower in the AGG group.
B. Reject hypothesis that the frequency of post-vaccinal encephalitis is lower in the AGG group.

if the patient had received AGG, the point was plotted one unit to the right of the preceding point; if the patient had received the placebo, the point was plotted one unit to the right and one unit higher than the preceding point. As soon as one of the straight lines (1 and 2) on the graph was crossed, the experiment was finished. If the last point were in region A, it could be concluded that AGG gives some protection against post-vaccinal encephalitis; if the last point were in region B, it could be concluded that there are no indications that AGG gives protection against post-vaccinal encephalitis.

The result of the experiment is indicated in the accompanying figure. After case no. 13 (see Table 2) had occurred, there were 11 cases in the placebo group and 2 in the treated group, so the last point falls in region A. Therefore the conclusion is that AGG gives some protection against post-vaccinal encephalitis.

At the time this conclusion was reached, the production of AGG was not yet sufficient to treat every vaccinee, so it was permissible to continue the observations and thus obtain a more accurate estimate of the effect of AGG. As soon as enough AGG could be produced for administration at all primary vaccinations, the investigation was stopped. By that time, the number of cases of disease in the placebo group was 13 and in the treated group 3. The best estimate of the reduction in the frequency of post-vaccinal encephalitis by administration of AGG is, on the basis of these figures, $\frac{13-3}{13} \times 100\% = 77\%$. The lower limit of the 95% (one-sided) confidence interval of this reduction is 28% (for details of the method of calculation, see Annex).

SUMMARY AND CONCLUSIONS

The value of AGG as a prophylactic against encephalitis after primary smallpox vaccination in adults was investigated in two large groups of military recruits that were comparable in all respects. A group of 53 630 men received an injection of 2 ml of AGG at the time of vaccination and a group of 53 044 men received a similar injection of a placebo; the two preparations were allocated at random.[1] Both groups of young men lived under the same conditions, which were designed to exclude exposure to harmful influences for the 18 days following vaccination.

In the subjects treated with AGG the local vaccination reaction followed no abnormal course. Admissions to hospital were based on a rise in temperature above 37.5°C. The difference between the admission rates in the treated and control groups was 4.7% ($P<0.0001$) in favour of the AGG group.

A group of 92 individuals who had received AGG at the time of primary vaccination were revaccinated after 2-4 years. The results of revaccination, estimated from the local reaction, did not differ from those in a group of 113 individuals who had not received AGG.

In the placebo group, 13 cases of encephalitis were observed, as compared with 3 in the AGG group. A sequential design of analysis was used. The best estimate of the reduction in the frequency of post-vaccinal encephalitis was 77%.

The frequency of the affection in the placebo group was about the same as that observed in the same period among an untreated group of 9000 recruits of the Royal Netherlands Navy (1 in 4500 primary vaccinations).

It is possible that the results would have been better if a larger dose of AGG had been used. The frequency of encephalitis after revaccination, which has been estimated at 1 in 50 000 in the Netherlands, indicates that a further reduction in the frequency of this complication after primary vaccination might be obtainable with an increase in dosage. It should be borne in mind, however, that the dose of AGG used must not interfere with the development of active immunity and should be consistent with the practicable rate of production of the material.

* * *

Administration of 2 ml of AGG at the time of primary vaccination was adopted as a routine practice by the Royal Netherlands Military Forces on 1 May 1959. In the period between that date and 1 May 1961, 30 000 primary vaccinations were performed. Only one of the vaccinated persons, who was treated on 28 June 1960, reacted with post-vaccinal encephalitis.

[1] See footnote on page 319.

Annex [1]

CALCULATION OF THE LOWER LIMIT OF THE 95% (ONE-SIDED) CONFIDENCE INTERVAL OF THE REDUCTION IN THE FREQUENCY OF POST-VACCINAL ENCEPHALITIS

It is assumed that the distribution of the number of cases of postvaccinal encephalitis is a Poisson distribution with a mean of μ in the placebo group and of $k\mu$ in the AGG group.

The probability of finding l cases of post-vaccinal encephalitis in the placebo group and m cases in the AGG group is

$$e^{-\mu} \cdot \frac{\mu^l}{l!} \times e^{-k\mu} \frac{(k\mu)^m}{m!}$$

which may be expressed, putting $l + m = n$, as

$$e^{-(k+1)\mu} \cdot \frac{k^m \mu^n}{l!\,m!}$$

$$= e^{-(k+1)\mu} \cdot \frac{\{(k+1)\mu\}^n}{n!} \cdot \left\{ \frac{n!}{l!\,m!} \cdot \frac{k^m}{(k+1)^m} \cdot \frac{1}{(k+1)^l} \right\}$$

The term between braces is the $l+1$th term of a binomial distribution with $p = \frac{1}{k+1}$.

If in an experiment, a cases of encephalitis have occurred in the AGG group and $n-a$ in the placebo group, then a conditional one-sided 95% confidence limit for k, under the condition that in both groups together n cases of post-vaccinal encephalitis occurred, may be defined as that value of k for which

$$\sum_{l=0}^{l=a} \left\{ \frac{n!}{l!\,(n-l)!} \cdot \left(\frac{1}{k+1}\right)^l \cdot \left(\frac{k}{k+1}\right)^{n-l} \right\} = 0.05$$

with $a = 3$, $n-a = 13$, $n = 16$.

With the aid of a table for the binomial distribution, a value of 0.58 is found for $\frac{1}{k+1}$, so $k = 0.72$. The upper limit of the 95% (one-sided) confidence interval for k is therefore $0.72\,\mu$, so the reduction in the frequency of post-vaccinal encephalitis is 28%.

As the total number of persons treated with AGG was 1% higher than the total number of persons treated with placebo, a slight correction ought in fact to be applied, which reduces this upper limit $k\mu$ to $0.71\,\mu$ and so increases the gain to 29%.

The above method for calculating the lower limit of the confidence interval is analogous to the method of Przyborowski & Wilenski (1939) for testing the equality of two Poisson parameters.

[1] Contributed by E. F. Drion, Statistics Department TNO.

RÉSUMÉ

Bien que l'étiologie et la pathogénèse de l'encéphalite postvaccinale soient encore inconnues, on peut essayer d'éviter cet accident de la vaccination antivariolique si l'on tient compte du fait qu'il survient beaucoup plus rarement lors de revaccination (1/50 000) que lors de primovaccination (1/4000). On a envisagé de prévenir l'encéphalite postvaccinale en associant à une primovaccination l'immunisation passive qui peut être obtenue, sans risques, par l'injection de gammaglobuline antivaccine. On a pu démontrer au cours d'une étude préliminaire que l'injection de doses diverses (1-6 ml) d'une solution à 16% de gammaglobuline antivaccine, 0-3 jours après une primovaccination, n'a aucun effet apparent ni sur la réaction locale ni sur l'immunité active, ni lors de revaccinations.

Une vaste expérience destinée à déterminer l'effet prophylactique éventuel de la gammaglobuline antivaccine a été effectuée dans l'armée et les forces aériennes néerlandaises où la vaccination antivariolique est obligatoire:

Un groupe de recrues recevrait 2 ml d'une solution à 16% de gammaglobuline antivaccine en subissant la primovaccination; un groupe témoin aussi important recevrait 2 ml de placebo. Ces recrues sont des hommes de 19 à 25 ans médicalement reconnus aptes au service militaire. Un nouvel examen médical, préalable à la vaccination, éliminait les sujets chez lesquels un risque accru de complications neurologiques pouvait être redouté. Afin d'éviter une fatigue physique ou mentale excessive, tous les sujets vaccinés étaient soumis à un contrôle sévère de leur activité pendant les 18 jours suivant une primovaccination.

L'administration de gammaglobuline antivaccine ou de placebo a été faite, sur un groupe aléatoire de ces sujets. Un personnel spécialement entraîné, employant une technique standard, a effectué les vaccinations. La gammaglobuline antivaccine a été préparée à partir de sang prélevé chez des volontaires en bonne santé, 4-6 semaines après une primovaccination subie avec succès, ou 3-4 semaines après une revaccination ayant produit une réaction pustuleuse nette.

L'expérimentation a duré 4 ans ½; elle a porté sur 106 674 recrues, 53 630 hommes formaient le groupe traité et 53 044 le groupe témoin.

Les résultats obtenus sont les suivants:

Les réactions vaccinales locales ont été normales chez les individus vaccinés ayant reçu 2 ml de gammaglobuline antivaccine. Cette dose eut un effet favorable sur la réaction fébrile; le nombre d'hospitalisations basées sur une élévation de température au-dessus de 37°5 est de 4,7% inférieur dans le groupe traité ($P < 0{,}0001$).

La gammaglobuline n'a pas eu d'effet sur le nombre de myocardites postvaccinales.

Le groupe traité présenta trois cas d'encéphalite postvaccinale, alors que le groupe ayant reçu du placebo en a présenté 13 (1/17 500 contre 1/4000). La fréquence des complications dans ce dernier groupe est à peu près semblable à celle observée durant la même période dans un groupe non traité de 9000 recrues de la marine (1/4500).

Il est estimé que la fréquence de l'encéphalite postvaccinale est ainsi réduite de 77%.

Dès le 1er mai 1959, l'administration de 2 ml de gammaglobuline antivaccine lors d'une primovaccination est devenue pratique courante dans les forces armées néerlandaises. Depuis cette date et jusqu'au 1er mai 1961, 30 000 primovaccinations ont été faites dans ces conditions; il n'y eut qu'un seul cas d'encéphalite.

REFERENCES

Bouwdijk Bastiaanse, F. S. van (1925a) *Bull. Acad. nat. Méd. (Paris)*, **94**, 815

Bouwdijk Bastiaanse, F. S. van (1925b) *Ned. T. Geneesk.*, **69**, 1194

Gispen, R., Lansberg, H. P. & Nanning, W. (1956) *Antonie v. Leeuwenhoek*, **22**, 89

Nanning, W. (1955) *Ned. milit. geneesk. T.*, **8**, 212

Przyborowski, J. & Wilenski, H. (1939) *Biometrika*, **39**, 313

Terburgh, J. T. (1932) *Algemeen Samenvattend Rapport van de Encephalitis Commissie*, The Hague, National Health Council

Vries, E. de (1960) *Postvaccinial perivenous encephalitis*, Amsterdam, Elsevier