

Observations

ON
PROPHYLACTIC INOCULATION AGAINST
PNEUMOCOCCUS INFECTIONS,

AND ON THE RESULTS WHICH HAVE BEEN
ACHIEVED BY IT.¹

By SIR ALMROTH E. WRIGHT, M.D., F.R.S.,
IN CONJUNCTION WITH

W. PARRY MORGAN, M.B. CANTAB., L. COLEBROOK,
M.B. LOND., AND R. W. DODGSON, M.D. LOND.

(Concluded from p. 10.)

SECTION IV.—Results Obtained by Therapeutic and
Prophylactic Inoculation of Pneumococcus
Vaccine.

WE have now completed the setting forth of the work which we did in connexion with the investigation of the antibacterial effects exerted by the blood upon the pneumococcus, and the testing and improvement of the methods for measuring it. We now go on to consider the results which were obtained when we passed from laboratory work to actual phylactic and prophylactic inoculation. We may begin with the former.

Treatment of Pneumonia by Vaccine-therapy.

It will be well to realise at the outset under what disabilities of ignorance we here pursued our work. The methods of blood examination which so often disappointed us when we were endeavouring to compare from day to day the opsonic power of the inoculated with that of the uninoculated natives, left us quite in the lurch when we set ourselves to make similar daily measurements in the case of our pneumonia patients. We were unable to trace upon the 50 immunisation curves which we plotted out in connexion with this work the effect of the doses of vaccine which we administered.

Accordingly, from first to last, we had to guide ourselves in our choice of doses and of the intervals between our doses only by *a priori* considerations and by the uncertain and flickering light which is furnished by temperature charts and the clinical symptoms. Influenced by the anticipation that the infected natives would be much more sensitive to pneumococcus vaccine than the uninfected native, we employed only doses of 2½ to 50 millions of pneumococci, and we conformed to the principle of giving in the less serious conditions larger, and in the more serious ones smaller, doses. In the ordinary case we repeated the dose at intervals of 24 to 48 hours.

These experiments—they have only the value of properly controlled reconnoitring experiments—were carried out in the hospital of the Witwatersrand Native Labour Association on tropical native patients. Many of these were, when admitted to hospital, already in an advanced stage of pneumonia. We accepted for our experiments only those who presented quite typical physical signs, and these were taken for treatment by vaccine-therapy or for treatment by the expectant method alternately, and strictly in the order in which they were admitted

to hospital. We took for every uninoculated patient who was treated by vaccine-therapy an uninoculated control, and for every inoculated patient an inoculated control.

As the net effect of our treatment, we obtained the results which are set out in the subjoined table:—

TABLE XI.—Showing the Case Mortality of Pneumonia in Tropical Natives treated respectively by Repeated Small Doses of Pneumococcus Vaccine and by Expectant Methods.

Therapeutic method employed.	Number of cases.	Number of deaths.
Vaccine-therapy	159	50
Expectant treatment	149	48

We would in connexion with these results specially emphasise (1) that they apply only to tropical natives who, having a very low power of resistance, have contracted virulent infection; and (2) that they apply only to inoculations carried out on such natives with the doses specified above.

What we have to say in connexion with the prospects of therapeutic inoculation in pneumonia will be better deferred till we come to summarise and comment upon the results obtained by inoculation.

Prophylactic Inoculation against Pneumonia.

We pass now to study the results which were obtained by prophylactic inoculation. The inoculations which we carried out or initiated range themselves under six mass-experiments.

Mass-experiment No. 1.—This mass-experiment was undertaken in the compound of the Witwatersrand Native Labour Association. This compound, familiarly known as the W.N.L.A. Compound, is, as has already been briefly explained, the receiving station at Johannesburg where the gangs of native labourers, who are recruited for the general service of the mines, are housed for three to four weeks before they are drafted off to their respective mines.

We confined our operations in this and the four next mass-experiments to the tropical natives. For it is especially these who are ravaged by pneumonia. In each case, two or three days after the arrival of a new gang, the natives were lined up. We then, dismissing any who showed symptoms of illness inoculated as they filed past us every alternate man, reserving in this way half of each gang to serve as controls. As the men came up to us the inoculated were made to pass on one side, and the uninoculated on the other; and lists were made of the depôt numbers of the two groups—each man's identification docket being at the same time ruled across with a diagonal line, which was red or blue according as he was inoculated or reserved as a control. After the lapse of eight to ten days the natives were again ranged up, and every man who had on the first occasion been inoculated was now reinoculated, while the controls were still kept as controls. The red or blue diagonal line on each man's docket was at the same time converted into a red or blue cross, and a corresponding entry was made upon the lists.

Proceeding in this manner between the months of October, 1911, and April, 1912, with each gang of tropical native labourers as it arrived, we inoculated a total of 5963 and reserved 5671 to serve as controls.

The doses which were employed varied with each gang and subgroup—for we were, as has been indicated above, engaged in following out from day to

¹ Being Part II. of a Report to the Witwatersrand Native Labour Association on the Results of an Inquiry into the Causation, Prophylaxis, and Treatment of the Pneumonia which affects the Native Labourers, and in particular the Tropical Native Labourers in the Rand Mines. Part I. was published in THE LANCET of Dec. 14th (p. 1633) and 21st (p. 1701), 1912.

day the effect exerted on the blood by different doses and different schemes of administration. The average amount of vaccine given in the two successive inoculations taken conjointly was something like 300 millions of pneumococci. It in no case exceeded 600 millions.

The results of the inoculations are furnished, so far as relates to the three or four weeks dating from the first inoculation, in the register of pneumonia cases and deaths kept in the hospital attached to the W.N.L.A. Compound. The clinical diagnosis was in each case made by the medical officer, Dr. George A. Turner, or the assistant medical officer, and by one of us (W. P. M.). In the fatal cases the cause of death was controlled by post-mortem examination carried out by the medical officer.

Information with regard to the subsequent history of the inoculated and uninoculated is furnished in two sets of returns. We have, first, the special monthly returns made to us from the mines—the so-called *red and blue monthly returns*. These record the number of cases of pneumonia and deaths from pneumonia occurring respectively in the red and blue group of tropical natives. We have, secondly, the returns of deaths, and specifically of deaths from pneumonia, rendered thrice monthly from the mines to the Chamber of Mines for the information of Government.

The “red and blue” returns proved unserviceable for our purpose, inasmuch as the depôt numbers of those who contracted, and died from, pneumonia were not supplied, and also because the results applying to the separate gangs were not kept apart. The Government returns, since they furnish the depôt numbers of those who succumbed to pneumonia, are those we depend upon for the later results set forth in the table below. The results of the mass-experiment, ascertained as explained above, are as follows:—

TABLE XII.—Showing the Number of Pneumonia Cases and Deaths from Pneumonia which occurred in the W.N.L.A. Compound between the Date of the First Inoculation and the Departure of the Natives to the Mines.

—	Number of men in the group.	Cases.		Deaths.	
		Number.	Percentage.	Number.	Percentage.
Inoculated	5963	147	2·6	50	0·83
Uninoculated ...	5671	198	3·5	87	1·53

TABLE XIII.*—Showing the Number of Deaths from Pneumonia reported from the Mines in each successive Month.

—	Number of men in the group.	Second month.	Third month.	Fourth month.	Fifth month.	Sixth month.
Inoculated ...	5963	11	19	12	10	7
Uninoculated...	5671	29	19	15	13	8

* In compiling this table the fact that the native whose death was recorded in the report from the mines had passed before us, and had been inoculated or set aside as a control, was verified by reference to our records; the period which had elapsed since the date of the first inoculation and his death being at the same time ascertained.

It will be seen that the inoculation exerted a marked effect for two months, but that after the end of the second month the inoculated had no advantage over the uninoculated.

To obtain the measure of the total effect of inoculation on the death-rate from pneumonia we may combine the figures for the deaths in Tables XII. and XIII.

TABLE XIV.—Showing the Effect which was exerted upon the Death-rate from Pneumonia in the first Two Months after Inoculation.

Inoculated ...	Number of men in the group.	Deaths.	
		Number.	Percentage.
... ..	5963	61	1
Uninoculated ...	5671	116	2

Mass-experiment No. 2.—After Mass-experiment No. 1 had been in progress for a certain time, and after it had appeared from the returns that favourable results were being obtained, we endeavoured to procure larger figures, such as would be really serviceable for statistical purposes, by undertaking “general inoculations” at the mines. We accordingly in December, 1911, and January, 1912, organised and ourselves took part in a number of “general inoculations” at the mines, and Dr. Turner, who helped us in this work, afterwards took independent charge of a number of others. We compute that in all 20,000 to 30,000 natives were in this way inoculated. Our intention was that the inoculated and the controls should, in connexion with these inoculations, have been chosen and registered in exactly the same way as had been done in the W.N.L.A. Compound; and we arranged for a special form of return in which the population of the mines should be divided up into (a) inoculated natives, (b) natives who were set aside as controls, and (c) natives who were excluded from the experiment either because they had joined later, or because they had for other reasons failed to put in an appearance at the inoculation parade. All sorts of difficulties, however, presented themselves in connexion with working out this scheme. It was found very difficult to get the records of the inoculated and controls accurately made when such large bodies of natives as were here in question were being dealt with. Again, the arrangements made for keeping track of the inoculated and uninoculated left in many places very much to be desired. Complications also presented themselves with regard to making proper allowance for natives who left the mines “time-expired” within the period of observation. Lastly, the inoculated turned out to be non-homologous with the controls, and there was—in contrast with what obtained in our other experiments—a sensible defect of homogeneity in the population of natives we were dealing with.

In connexion with the comparability of the inoculated and the controls it may be explained that the native labourers on the Rand come from as far south as the Cape, and from as far north as the Equator; and that there are between the different races of natives at the mines great differences with respect to tractability and susceptibility to pneumonia, the tropical natives being at once the most tractable and the most susceptible to pneumonia, and the East Coast natives, as we are informed, much more difficult to handle and at the same time more resistant to pneumonia. It will be readily understood that under these circumstances the inoculated group would tend to be more largely composed of the more tractable and, as it happens, more susceptible tropical natives, and the uninoculated group to be composed of the less tractable and, as it happens, less susceptible East Coast natives.

In connexion with the homogeneity of the population operated upon, it is to be observed that the fresh arrivals are (as will be seen from the figures for the uninoculated in Tables XII. and XIII., XV. and XVII.) the most susceptible to pneumonia, and that those who have been longer upon the mines have become more resistant to pneumonia. By consequence every group which is chosen from the native population, without reference to length of residence on the mines, will comprise persons of very different degrees of resistance.

As soon as these considerations had, one after the other, come home to us, we decided to bring this particular mass-experiment to a close, and to jettison, as open to fallacy, such statistical returns as had already been sent in to us in connexion with the experiment.

If, as we cannot in view of our other experience doubt, this mass-experiment gave good results, we suggest that the advantage was reaped in the form of a diminution in the general death-rate from pneumonia on the Rand.

Mass-experiment No. 3.—Having learned from experience in Mass-experiment No. 2 the difficulties which have to be confronted and the fallacies which have to be avoided in connexion with a general inoculation, we set ourselves to organise such an experiment upon better lines. The mass-experiment here in question was begun in May, 1912. It consisted in a series of general inoculations undertaken in 20 mines² and limited to tropical natives who had, in the season 1911-12, passed out to the mines from the W.N.L.A. Compound. In view of the fact that it had been shown in Mass-experiment No. 1 that there was, after two months, no difference between inoculated and uninoculated, the whole of the tropical natives of the year, with the exception of those few who left the compound for the mines in March and April,³ were regarded as, for our purposes, homologous.

In each mine three general inoculations were undertaken, approximately a month intervening between the first and the second, and again between the second and the third inoculation; and the dose of vaccine was uniformly 150 million pneumococci. On the *first* occasion approximately half of the tropical natives were inoculated, and half were left as controls—giving a group of 3975 inoculated and a group of 4769 uninoculated. Among these last were counted in a certain number who were actually at work on the mine, but who for one reason or another were not actually forthcoming at the first parade. At the *second* general inoculation, half of those who had on the first occasion served as controls were inoculated; and of those who were on that occasion inoculated one moiety was reinoculated, while inoculation was withheld from the other with a view to find out how long the effect of the previous inoculation would make itself felt. At the *third* general inoculation, again, half of those who functioned at the second inoculation as controls were inoculated, and nearly all those who were previously inoculated were reinoculated.

Quite special care was devoted to ensuring accuracy in the records, the procedure adopted being as follows. For each mine two lists were prepared. On the first (hereafter called the "depôt list") the "depôt numbers," with which the natives leave the W.N.L.A. Compound, were arranged in serial order, the corresponding "mine numbers,"

which are given to the natives on arrival at their mines, being entered in the second column. On the second list (hereafter called the "mine list") the mine numbers were set down in serial order, and the corresponding depôt numbers were entered in the second column. This done, the depôt list was taken in hand by us, and we inserted in the third column, opposite the numbers, alternately a red or a blue diagonal line—the red line to indicate that the native was to be inoculated, the blue that he was to serve as a control. Corresponding entries were then made on the mine list.

When visiting the mine for the purpose of the general inoculation the natives were identified by their mine numbers as they passed up from their work, and they were inoculated or sent on uninoculated, according as their numbers were marked in red or blue, and the diagonal lines on the list were at the same time converted into crosses to show that these natives had been dealt with. Corresponding crosses were afterwards made upon the depôt list. The returns were made monthly by the medical officers of the mines on printed forms specially issued for this purpose. The return gave in connexion with each patient admitted to hospital his depôt number, the date of his admission, the diagnosis, and the date of his discharge or death.

In Table XV. we have grouped the results under the headings of results in the *first, second, third, and fourth* months. We have included in the results obtained by inoculation in the first month, not only the results which refer to the 3975 inoculated in the first general inoculation, but also the figures which refer to the natives who were inoculated for the first time at the second and third general inoculations. Moreover, in the case where a man was inoculated more than once we have set down in the "results obtained in the first month after inoculation" those which apply to him for the month following each of his several inoculations. For we find by analysis of the figures that the inoculation of men who have been inoculated one month previously with 150 millions gives neither better nor worse results than are obtained where men are inoculated for the first time.

We have dealt in a precisely similar fashion with the results which apply to the uninoculated. For instance, when, in making up our results for the first month, we come upon a man who was at each of three successive general inoculations taken as a control, we enter him in our statistics three times over (once for each several month) in order that he may serve as a control for the men who were inoculated at the first, second, and third inoculations respectively. Similarly, when we come upon a man who was inoculated for the first time at the third general inoculation, we include him twice over in our controls. And when we come upon a man who was inoculated for the first time at the second general inoculation, we include him once in our controls. We follow, *mutatis mutandis*, precisely the same procedure when dealing with the returns which apply to the second, third, and fourth months.

It will be seen that with the very small dose of vaccine which here came into application a very striking advantage was achieved in the first month after inoculation, but that advantage had nearly passed away by the end of the third month. The records are not continued beyond the fourth month because the mass-experiment next on our list was then begun.

² The mines chosen for the experiment were those which had received the largest number of tropical natives.

³ These were excluded from the experiment and left out of the record.

TABLE XV.—Showing Results for Four Successive Months after Inoculation. Results for the First Month.

	Number of men in the group.*	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Per-centage.	Number.	Per-centage.
Inoculated	10,626	125	1.1	22	0.21
Uninoculated	10,508	216	2.05	40	0.38
Results for the Second Month.					
Inoculated	6,787	76	1.12	15	0.22
Uninoculated	8,380	128	1.5	25	0.3
Results for the Third Month.					
Inoculated	6,103	59	0.96	13	0.21
Uninoculated	7,823	92	1.2	22	0.28
Results for the Fourth Month.					
Inoculated	6,103	44	0.72	16	0.26
Uninoculated	7,823	63	0.87	20	0.25

* In view of the fact that the corrections which would be applicable under the heading of deaths and repatriations would be quite insignificant, we have not troubled to deduct them from the numbers of the inoculated and uninoculated.

Mass-experiment No. 4.—This experiment consisted in a general inoculation carried out in November in 18 out of the 20 mines which were in question in the last experiment. It relates to those tropical natives who belonged to gangs which passed through the W.N.L.A. Compound in 1912, and who were accordingly due to remain in the mines till at least the end of January, 1913. Those who had in the last experiment served as controls were retained as such, and the rest were reinoculated—in each case with a dose of 1000 millions of pneumococci, grown in part on serum broth and in part on glucose serum broth. In this way there was obtained a group of 610 uninoculated, which for the purpose of such comparisons as those we are here making was undesirably small, and a group of 2322 inoculated. The results as ascertained from the returns rendered on the printed forms referred to in connexion with the last experiment were as follows:—

TABLE XVI.—Setting Forth the Result Obtained for the Period of Five Months after the Date of the Inoculation.

	Number of men in the group.	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Per-centage.	Number.	Per-centage.
Inoculated	2322	70	3.0	20	0.86
Uninoculated	610	21	3.4	8	1.3

The question as to why larger advantage was not here reaped from inoculation is reserved for discussion in our summary of results.

Mass-experiment No. 5.—This experiment was undertaken upon the tropical natives who arrived in the compound of the W.N.L.A. between the middle of August and the end of November, 1912. The chief objects that it had in view were: (a) the determination of the optimum dose of pneumococcus vaccine for prophylactic uses, and (b) the decision of the question whether cultivations on glucose serum broth furnished a better vaccine than cultures on the ordinary serum broth. The inoculations were carried out exactly as in the case of Mass-experiment No. 1, with the difference that only every fifth native was taken as a control. The procedure adopted with regard to dosage was to take for the

general inoculation in each case doses which had been previously ascertained to be perfectly safe, and then to reconnoitre by inoculating a small group with larger doses.* Advancing in this manner we obtained for study a series of six groups.

The general results may be summarised as follows: Employing a vaccine prepared by cultivating the pneumococcus on blood broth and a dose of 250 millions, we obtain, for a period of one month after inoculation, a reduction of the incidence from 7 per cent. in the controls to 3.7 per cent. in the inoculated; and a reduction of the death-rate from 2.9 per cent. in the controls to 1.5 per cent. in the inoculated, that is to say, in each case a reduction equivalent to about 50 per cent. With a dose of 500 millions of the same vaccine we obtain, for the first three months after inoculation, a reduction of about 25 per cent. in the incidence and nearly 50 per cent. of the death-rate. With 1250 millions of the same vaccine we obtain a much less favourable result: a reduction, on a period of three months, of 30 per cent. in the incidence and of only 20 per cent. in the death-rate. We may presume that the dose here employed was too large. Employing a vaccine prepared by cultivating a pneumococcus on glucose blood broth we obtain, for a period of two months, with a dose of 500 millions a reduction of 50 per cent. in the incidence and of 40 per cent. in the death-rate. With a dose of 1000 millions we obtain,

TABLE XVII.†—Showing the Results obtained by the Inoculation of Various Doses of Pneumococcus Vaccine grown on Blood Broth and Glucose Blood Broth respectively.

	Number of men in the group.	First month.		Second month.		Third month.		Fourth month.		Fifth and sixth months.	
		Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.

(A) Results obtained by the Inoculation of 250 millions of Pneumococci grown on Blood Broth.

Inoculated ...	646	24	10	17	5	14	4	9	2	16	5
Uninoculated ...	626	44	17	17	5	12	4	15	5	16	6

(B) Results obtained by the Inoculation of 500 millions of Pneumococci grown on Blood Broth.

Inoculated ...	769	25	8	16	4	17	2	14	4	19	8
Uninoculated ...	764	46	19	21	6	17	5	18	5	20	6

(C) Results obtained by the Inoculation of 1250 millions of Pneumococci grown on Blood Broth.

Inoculated ...	1582	37	17	40	10	28	10	17	6	44	13
Uninoculated ...	791	23	10	31	8	21	6	12	3	14	7

(D) Results obtained by the Inoculation of 500 millions of Pneumococci grown on Glucose Blood Broth.

Inoculated ...	463	18	10	7	1	9	3	7	2	7	5
Uninoculated ...	457	35	14	14	5	10	3	12	4	10	4

(E) Results obtained by the Inoculation of 1000 millions of Pneumococci grown on Glucose Blood Broth.

Inoculated ...	650	20	6	20	3	10	2	6	3	14	3
Uninoculated ...	595	37	16	18	6	15	4	15	4	14	4

(F) Results obtained by the Inoculation of 2500 Pneumococci grown on Glucose Blood Broth.

Inoculated ...	1582	47	17	42	8	28	5	21	10	35	8
Uninoculated ...	791	23	10	31	8	21	6	12	3	14	7

* We found in these experiments that doses up to 40,000 millions of pneumococci produced nothing more than a very slight constitutional disturbance and a very small rise of temperature. This is in good accord with the generalisation (*vide supra* Section II) that what counts in the case of an inoculation is not the actual quantum of vaccine we incorporate, but the quantum of antigen set free from it in the organism of the patient.

† It is to be observed that the results of those inoculated with reconnoitring doses are excluded from consideration, and that the uninoculated who serve for controlling the effect of one dose are often the self-same individuals as serve for the controlling of another dose.

over a period of three months, a reduction of 30 per cent. in the incidence and of over 60 per cent. in the death-rate. With a dose of 2500 millions we again obtain less satisfactory results; a reduction of just over 20 per cent. in the incidence, and a reduction of 35 per cent. in the death-rate.

There can be extracted from the statistical data which are available in connexion with this mass-experiment, not only conclusions bearing on the question of the relative efficacy of the various doses of vaccine which were administered, but also valuable information bearing on the question of the production of a negative phase—information which has, as we shall see, an important bearing on the question of the utilisation of vaccine in the treatment of pneumonia. The data which seem to us important from this point of view are set out below in the form of a table.

The facts which are set forth in this table are, as will be seen, very remarkable. Associating together the figures which apply to Groups A, B,

TABLE XVIII.

	Number in group.	Number of cases of pneumonia which developed.													
		First day.		Second day.		Third day.		Fourth day.		Fifth day.		Sixth day.		First six days.	
		Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Group A (inoculated with 250 millions)	646					1	1	2	1					3	2
Control group	626	1	1	4	1	3	1	2	2			2	2	12	7
Group B (inoculated with 500 millions)	759			2		1	1			3	1	1		7	2
Control group	764	1	1	5	2	3	1	2	2			2	2	13	8
Group C (inoculated with 1250 millions)	1582	8	4	2		1	1	1						12	5
Control group	791	1	1	2	2							1		4	3
Group D (inoculated with 500 millions glucose vaccine) ...	463	1	1			1								2	1
Control group	457	1	1	3	1	3	1	1	1			2	2	10	6
Group E (inoculated with 1000 millions glucose vaccine) ...	650			1		2		2				1		6	
Control group	595	1	1	4	2	3	1	1	1			2	2	11	7
Group F (inoculated with 2500 millions glucose vaccine) ...	1582	7	3	11	2	1	1	3		2	2			24	8
Control group	791	1	1	2	2							1		4	3

D, and E; i.e., the groups which received doses up to 1000 millions of pneumococci, we find that, in the first four days after inoculation, 2500 inoculated had an incidence-rate of 0.52 per cent., and a death-rate in connexion with these cases of 0.16 per cent., while 750⁴ controls had an incidence-rate of 1.4 per cent., and a death-rate in connexion with these cases of 0.84 per cent. In other words, the uninoculated had an incidence-rate nearly three times and a death-rate five times greater than the inoculated.

Again, associating together the figures which relate to Groups C and F—groups which received doses of over 1000 millions of pneumococci—we

find that 3200 inoculated had for the same period an incidence-rate of 1.1 per cent., and a death-rate in connexion with these of 0.32 per cent., while 800 controls had an incidence-rate of 0.4 per cent., and a death-rate also of 0.4 per cent.

Two important conclusions follow: the *first* is that pneumococcus inoculation undertaken with doses up to 1000 millions had a marked effect in aborting pneumonia and in diminishing the case mortality. Or we may phrase it otherwise. Vaccine therapy as applied to the treatment of pneumonia is successful when doses of 250 to 1000 millions are given in the incubation stage of the disease. The *second* conclusion is that inoculation undertaken with doses of over 1000 millions of pneumococci may perhaps temporarily increase the incidence-rate of pneumonia.

It is perhaps of interest to point out that these conclusions are essentially the same as those formulated in connexion with plague vaccine by Mr. Haffkine, immediately after he had carried out his first mass-experiment in the Byculla Jail, Bombay, in 1898. In that experiment, as in the mass-experiment we are here dealing with, a decisive difference in favour of the inoculated half of the population manifested itself already within 24 hours. And the view that Mr. Haffkine maintained (in contravention to that held by one of us) that plague vaccine does not produce a negative phase, and that it has the power of aborting an incipient attack, was afterwards established by evidence accumulated by Miss Alice Corthorn, M.D.,⁵ and Surgeon-General W. B. Bannermann, I.M.S.⁶ In connexion with this all that requires to be said is that the generalisations in Section II. of this Report—generalisations which have been reached only after years of further work—have made it intelligible that a negative phase should manifest itself with large doses of typhoid vaccine, a vaccine which is easily broken down in the normal organism, and again with all vaccines after the organism has, by foregoing immunising response, acquired bacteriostatic power, and that this phase should make default in the uninfected organism, and in the early stages of infection when vaccines, such as plague vaccine and pneumococcus vaccine which are with difficulty broken down in the body, are inoculated.

In concluding this account of the results obtained in Mass-experiment No. 5 we may profitably advert to one more general consideration. It is, as will presently be brought out more fully in Section V., reasonable to expect that an effective inoculation will give an additional bonus in the form of a diminution in the morbidity which comes upon the record under the heading of "Other Diseases." In point of fact, the records which relate to the particular mass-experiment we are here discussing show such a reduction. We have our bonus in the form of a 15 per cent. reduction in the "other diseases" of the inoculated, the figures being: *inoculated*, 6224; *uninoculated*, 1545. Cases of sickness other than pneumonia: in *inoculated*, 2154; in *uninoculated*, 620.

We now pass to our sixth and last mass-experiment.

Mass-experiment No. 6.—This mass-experiment was undertaken upon the natives employed in the Premier Diamond Mine—a mine which, despite the fact that it employs no tropical labour, has always suffered very severely from pneumonia. We began

⁴ This figure is arrived at by taking the actual number of men who served as controls for Groups A, B, D, and E.

⁵ Brit. Med. Jour., Jan. 25th, 1902.

⁶ Ibid., Sept. 14th, 1901.

with a general inoculation on Jan. 21st, 1912, inoculating at a sitting about 4000 natives. The experiment thus begun was followed up by a methodical inoculation of the recruits who joined the mine. These inoculations were very admirably organised, carried out, and recorded by Dr. J. C. A. Rigby, who was very ably assisted by Mr. H. P. Sheridan. From Jan. 21st onwards till March 15th, 1912, every second native was inoculated as he arrived at the mine. From that date onwards only every third man was kept as a control, and gradually as it became more and more evident that good results were being obtained an increased proportion of the recruits were inoculated.

At the outset the dose which was employed was 200 million pneumococci, and gradually as it became clear from the results that were coming in from Mass-experiment No. 5 that the employment of larger doses was indicated the doses were gradually increased to 250 million, then to 500 million, until finally a dose of 1000 million was reached.

Returns which were very carefully prepared were furnished to us every month, and we were further, at the end of the first six months, and again at the end of the first year of the experiment, furnished with a detailed synopsis of the results. These returns are our authority for the facts set forth below.

TABLE XIX.—Showing the Results for the Whole Native Population of the Mine for the Year beginning Jan. 22nd, 1912, and ending Jan. 21st, 1913.

	Daily average strength of the group.	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Per-centage.	Number.	Per-centage.
Inoculated	9909	508	5.13	154	1.55
Uninoculated	4520	467	10.33	145	3.21

We subjoin also, for reasons that will presently appear, another statistical record which excludes all those who were on the mine on Jan. 21st, 1912, and takes into account all the natives who came to work on the mine during the next 12 months. It may be remarked that the fact that the native at this mine usually works on a six months' contract would make the daily average population equivalent to about half the number of the natives who join in the year.

TABLE XX.—Showing for the period Jan. 22nd, 1912, to Jan. 22nd, 1913, the Results for the Natives who came in that year to work on the Mine.

	Number of natives who joined the mine.	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Per-centage.	Number.	Per-centage.
Inoculated	17,431	376	2.16	120	0.7
Uninoculated	6,771	348	5.14	120	1.77

Finally, in connexion with the mass-experiment here in question, we may give the figures for the corresponding period relating to the incidence and death-rate of "other diseases" in the inoculated

and uninoculated sections of the population. These figures are as follows: *Inoculated*, average daily strength, 9909; incidence rate, 47.2 per cent.; death-rate, 0.93 per cent. *Uninoculated*, average daily strength, 4520; incidence rate, 106.6 per cent.; death-rate, 1.90 per cent.

SECTION V.—General Survey of the Results obtained by Therapeutic and Prophylactic Inoculation of *Pneumococcus Vaccine*; and Critical Comment.

Vaccine-therapy of Pneumonia.

In connexion with the vaccine-therapy of pneumonia we have, on the one hand, the fact that inoculation in the form of small doses frequently repeated was absolutely ineffective (Table XI.); and, on the other hand, the fact that inoculation in the form of a single large dose, administered in the incubation period, often arrested the disease and averted death (Table XVIII.).

That the difference of dose determined the difference of event is to us as good as certain. Let us—recalling to mind the general propositions formulated in Section II.—here take note of the fact that the doses which we found inoperative were doses from which there could, at best, have been expected that they should elicit a local immunising response. Further, let us note that the evocation of such response would be dependent upon a sufficiency of antigen passing into solution in the lymph at the seat of inoculation.

Lastly, let us note that it is quite likely that microbes which are ingested by phagocytes may, from the point of view of the immunising reaction, be left quite out of regard.⁷ In connexion with this it is almost superfluous to point out that when comparatively small numbers of microbes are inoculated, and when they come into contact with a lymph which possesses opsonic power, but only inappreciable bacterioclastic power, they will almost certainly sooner or later be ingested by phagocytes.

In general contrast with all this would be what would happen when a large dose of vaccine is inoculated. In this case the microbes would be carried on into the main lymphatic current or blood-stream, with the result that inevitably some would escape phagocytosis, and inevitably some of these would, even if the blood had but very little bacterioclastic power, be broken down. And there would supervene upon the convection of the antigen to the tissues through the blood a systemic immunising response.

As we see no reason to suppose that the conditions appreciably alter, and as we know that the bacterioclastic power of the blood does not sensibly increase when pneumonia develops, we think it reasonable to expect that the favourable results which were obtained by the inoculation of doses of 250 to 1000 millions of pneumococci would repeat themselves if this treatment were applied in the early stages of pneumonia. We were prevented from undertaking a therapeutic mass-experiment upon these lines in the season 1912-13 by the fact that we were then engaged upon Mass-experiment No. 5 (that which furnished the data we have here been reviewing), and had to be on our guard against falsifying the results it was giving by any therapeutic interference.

⁷ We hark back here to an objection which was long ago (as we think inappositely, because the blood fluids exert a bacteriolytic effect on the cholera vibrio) brought forward by Metchnikoff in connexion with Ferran and Haffkine's anti-cholera inoculations.

Prophylactic Inoculation against Pneumonia.

The comparative statistics which have been set forth above testify, as has been seen, in every case to a reduction in the incidence-rate and death-rate of pneumonia in the inoculated.

In adjudicating upon a procedure of prophylactic inoculation the following general theses must be taken into account.

1. The advantage derivable from a prophylactic inoculation will be limited by the patient's power of immunising response. In accordance with this, one would not expect to achieve as much by inoculation in a naturally non-resistant population—such as that represented by the tropical native labourers on the Rand—as in a more resistant population—such as is, by common repute, represented by the native labourers on the Premier Mine. We may, perhaps, bring into relation with this consideration the fact that we have, as the result of the application of prophylactic inoculation to the tropical natives on the Rand, in *Mass-experiment No. 1* (Tables XII. and XIII.) a reduction of 37·5 per cent. in the death-rate of the inoculated upon an observation-period of six months; in *Mass-experiment No. 3* (Table XV.) a reduction of 31 per cent. in the death-rate of the inoculated upon an observation-period of four months; and in *Mass-experiment No. 5* (Table XVII., Group E) a maximum reduction of 50 per cent. in the death-rate of the inoculated upon an observation-period of six months; while we have upon the Premier Mine (*Mass-experiment No. 6*, Table XX.) upon a 12 months' observation-period a reduction of 60 per cent. in the death-rate for the inoculated.

2. The advantage derivable from prophylactic inoculation will depend upon the degree to which the population to which it is to be applied has already run the gauntlet of the particular microbic infection in question. In accordance with this, one would expect greater advantage from inoculation when applied to a population newly arrived in the field of infection, than from inoculation applied to a population which had been long in such a field *continuously* exposed. It falls in with this, that while we have in the inoculated in *Mass-experiment No. 5*, Group E—an experiment in which the uninoculated had an incidence-rate of 15 per cent., and a death-rate of 5 per cent. over a five-month period—a reduction of 35 per cent. in the incidence and of 55 per cent. in the deaths; we have in the inoculated in *Mass-experiment No. 4*⁸—an experiment in which the uninoculated had an incidence-rate of 3·4 per cent. and a death-rate of 1·3 per cent. for the same period—a reduction of only 10 per cent. in the incidence-rate and of 34 per cent. in the death-rate. We may further note that we have, in connexion with *Mass-experiment No. 6*, in the case of the inoculated a reduction in the incidence-rate of 50 per cent., or 58 per cent., and a reduction in the death-rate of 52 per cent., or 61 per cent., according as we take as our controls (as in Table XIX.) the population already on the mine, or (as in Table XX.) the population of new arrivals.

3. Where in comparative statistics we find that the difference between the inoculated and the uninoculated is after a certain time effaced, this does not necessarily indicate that the immunity of the inoculated is diminishing. We may be witnessing, instead of a descent of the inoculated to the level of the uninoculated, an ascent of the uninoculated to

the level of the inoculated. This is, presumably, the true interpretation of the fact that our inoculated natives displayed only for a comparatively short period an advantage over the uninoculated. For we have uniformly, in all our records (*Mass-experiments Nos. 1, 3, and 5*; Tables XII. and XIII., XV., and XVII.), and therefore presumably independently of any change in the external conditions—instead of a progressive falling off in the incidence-rate and death-rate of pneumonia in the inoculated, a progressive improvement in the incidence and death-rate in the uninoculated.

The point of interest which here suggests itself is the question as to how the ascent of the uninoculated to a higher level of immunity, and the accompanying progressive improvement in the figures for the inoculated, which is a feature of all the statistics, is to be accounted for. Two alternative hypotheses here suggest themselves. The attainment of a higher level of immunity may be explained by supposing that the most susceptible individuals have been weeded out by death from each group. But this is not a very acceptable hypothesis, for it is hard to believe that infection can ever be distributed over a population in so uniform a manner as punctually to pick out and kill all the more susceptible individuals. It is much more probable that the progressively increasing resistance in both the inoculated and uninoculated groups is achieved by processes of self-immunisation consequent upon minor infections which affect practically the whole mass of the population. We have what we think presumptive proof that such agencies are at work in the fact, already adverted to above, that there were, in practically every group of four to six uninoculated natives whom we employed as controls, some who were almost certainly suffering from minor pneumococcus infections. Not only does this theory furnish, as it seems to us, a satisfactory explanation of the progressive improvement in the figures for both inoculated and uninoculated, but it puts into our hands, as we think, a clue which may guide us in our search for the optimum dose of a vaccine for prophylactic use. In the case where we institute a comparative experiment—and we have the results of such a comparative experiment set out in Table XVII., Groups A and E—employing in one group (let us call it *Group No. 1*) a smaller, and in another group (let us call it *Group No. 2*) a larger dose; and where we then find that in *Group No. 1* the figures, taken when those for the uninoculated become equally good, are inferior to those afterwards reached; and that in *Group No. 2* the figures, taken again when those for the uninoculated become equally good, are not afterwards improved upon—we may legitimately infer that in *Group No. 1* prophylactic inoculation left something undone which was afterwards achieved by self-immunisation; and that in *Group No. 2* prophylactic inoculation accomplished, so far as appears, all that self-immunisation was capable of achieving. It will be realised that this amounts to saying that the optimum dose, or series of doses, of vaccine is that which produces an immunising response which is incapable of any further reinforcement; and that we ought to aim at effecting by prophylactic inoculation all that living in the presence of infection, and having actual dealings with infection, is capable of achieving.

4. Comparative statistics furnish only a very incomplete account of the profit earned by any successful prophylactic inoculation. It has among

⁸ In this *mass-experiment* the dose of vaccine employed was the same as that in *Mass-experiment No. 5*, Group E, and the culture medium employed in making the vaccine was also largely the same.

statisticians been too much the habit to give credit only for the profit shown upon comparative statistics, and to disallow credit for maintained advantage unless proof is produced that the incidence and death-rates of the disease have been, as the ordinary statistician would wish, maintained in the uninoculated section of the population. Examples of this method of auditing profits are furnished by the fact that when, in connexion with small-pox vaccination, the statistical records for France, which is very incompletely, and Germany, which is very completely vaccinated, are contrasted; or when, in connexion with typhoid inoculation, the condition in the army in India before typhoid inoculation is contrasted with its condition to-day, when the large bulk of the British troops are inoculated; or when, in connexion with that same process, a comparison is made between the statistics for the Jacksonville Camp in the Spanish-American War, where out of a strength of nearly 11,000 United States troops, all being uninoculated, at least 1729 contracted typhoid, and the statistics for the San Antonio Camp on the infected Mexican frontier, where nearly 13,000 United States troops, who were all inoculated, were massed with only one case of typhoid⁹; the comparison is in each case disallowed on the ground that there were not sufficient uninoculated controls interspersed among the inoculated, or that the contrasted populations were not quite homologous, or that the conditions to which they were exposed were not exactly alike. The statistical auditor who refuses to give any credit upon vouchers which have been left in some point incomplete is, of course, keeping himself well within the law. But he is leaving quite out of regard the equities.

When the question as to how we should evaluate the results of an effective inoculation process (and we may here deal specifically with pneumococcus inoculation) is regarded from this point of view—in other words, when we take a broad view of the probabilities—it will become clear that it would be altogether proper to claim credit:—*in connexion with the inoculated*: (a) for any diminished incidence and any diminished death-rate from pneumonia which is attested by comparative statistics for inoculated and uninoculated; (b) for any diminished incidence and death-rate from other pneumococcic infections (whether diagnosed as such, or undiagnosed) which come upon the record; and (c) for any diminished incidence and death-rate from infections which were not due to the pneumococcus, but were directly consequent upon pneumococcic infection. Further, *in connexion with the uninoculated* section of the community, credit may equitably be claimed (d) for any diminution in the incidence-rate and the case-mortality of pneumococcic infections—for the former because a reduction in the number of pneumococcic cases in the inoculated would diminish the general volume of infection; for the latter, because a reduction in the virulence of the infection might reasonably be expected from the diminished “passaging” (i.e., transference from case to case) of the infective microbe.

It is to be noted that it is only the establishment of the general principle that we may anticipate profits under each of these headings, and that these profits cannot equitably be left out of account,

which is here vital. The matter of real concern in connexion with any effective inoculation procedure is that by it we are transported out of a vicious circle—a *circulus vitiosus* of infection and non-resistance, into a “propitious circle”—a *circulus felix* of increased resistance and diminished infection. In comparison with the establishment of this, it is a small matter that, when fairly entered upon a propitious circle, it becomes impossible to tell how much of the sum-total of effects is due to inoculation and how much to other causes.

With these preliminary explanations and reserves we may here subjoin a further table which has reference to the mass-experiment on the Premier Mine.

TABLE XXI.—Showing for the Whole Native Population of the Premier Mine the Incidence and Death-rate for Pneumonia; the Incidence and Death-rate for “Other Diseases”; and also the Number of Working Days Lost through Illness; for the Months February to May,* in 1911, 1912, and 1913 respectively.

—	1911	1912	1913
Population (daily average strength)	10,426	12,549	15,284
Proportion of the population inoculated	0	About 50 per cent.	About 92 per cent.
Incidence-rate of pneumonia	4 per cent.	1·28 per cent.†	0·74 per cent.†
Death-rate from pneumonia	0·97 per cent.	0·31 per cent.	0·14 per cent.
Incidence-rate of other diseases	31 per cent.	20·7 per cent.	14·4 per cent.
Death-rate from other diseases	0·51 per cent.	0·38 per cent.	0·34 per cent.
Number of working days lost per 100 native labourers	275	177	131

* We have been furnished with data for this comparison only up to May, 1913.

† In 1912 the incidence-rate was 0·86 per cent. for the inoculated and 1·7 per cent. for the uninoculated. In 1913 it was 0·6 per cent. for the inoculated and 3 per cent. for the controls.

SECTION VI.—Concluding Considerations and Recommendations with Regard to the Measures to be taken to Combat the Pneumonia on the Rand.

In considering what measures ought to be taken to combat the pneumonia on the Rand it is essential to start with a proper appreciation of the character and natural history of the disease. The salient facts in connexion with the pneumonia which affects the native labourers on the Rand are as follows:—

The disease is—as investigation, and in particular the investigation made by Dr. Turner in Tropical Africa, has shown—unknown, or practically unknown, in the native kraals. The disease has no special relation to the mining work on the Rand. It takes no heavier toll of the natives at work in the deep-level mines of the Rand than of those employed on the Premier Mines on open workings. Moreover, the disease is seen at its very worst in the compound of the W.N.L.A. among the newly arrived natives who have not yet begun their work on the mines. Again, the prevalence of pneumonia and other pneumococcic infections among the natives in the mines of the Transvaal can have no special relation to its climate or to its elevation above the sea level; for these infections caused a very heavy mortality among the African natives working upon the Panama Canal at sea level. And they also cause very serious loss of life among the negro labourers and soldiers in Rhodesia, the French African Colonies, the Egyptian Soudan, and

⁹ Russell: United States Army Medical Department, Bulletin No. 2, January, 1913, p. 11.

elsewhere. Finally, we have the very material fact, which has been brought out in this report, that the blood of the African native is, so far as relates to its power of phagocytosing and killing the pneumococcus, very inferior to that of the European, and that the capacity for immunising response is also much less in the African than in the European.

These considerations make it practically certain that the prevalence of pneumonia on the Rand is to be ascribed to the bringing together into close contact in compounds of a population which has, as a racial character, a low resisting power to the pneumococcus. If this is so, it is obviously a circumstance which ought to dictate our plan of attack, and to determine in particular what place in our scheme of operations ought to be taken respectively (a) by measures which aim at preventing the convection of pneumonia from man to man; (b) by measures which aim at holding off influences which might impair the natives' resistance to infection; and (c) by measures which aim at increasing the natives' resistance to infection.

(a) Under the heading of "measures for avoiding the convection of infection from man to man" would come: measures for the earliest possible detection and isolation of cases of pneumonia; measures for the disinfection of the sleeping quarters from which such cases have been removed; measures for diluting the infective matter in these sleeping quarters by schemes of ventilation; and lastly, measures for the quarantining of recovered pneumonic patients with a view to the prevention of a spread of infection from these. With regard to these, we may remark that, while we see no reason to doubt that each of these measures would in its degree counteract the spread of infection, we have grave doubts as to whether they could ever be made effective measures for combating pneumonia on the Rand. We are taking into consideration here, *first*, the fact that it would be a very difficult thing to carry out upon the Rand measures for the early detection and subsequent quarantining of pneumonic cases; *secondly*, the fact that we have on the Rand not only to deal with pneumonia, but also with very numerous cases of lighter forms of pneumococcal infection; and, *thirdly*, the fact that the pneumococcus lives saprophytically on the mucous membrane of a majority of healthy men. Moreover, in connexion with the question of the adoption of measures for preventing the spread of pneumonic infection from man to man, it will be well never to leave out of sight the fact that given a population which, like a European population, possess a relatively high resistance to the pneumococcus, all such measures can be dispensed with.

(b) Coming now to "measures for holding off influences which might impair the native normal resistance to infection"—and we have in view here such a measure as the provision of "change houses"¹⁰ for safeguarding the native against chills—we are of opinion that the place of such measures in a plan of campaign against pneumonia is at best a very subordinate one. In this connexion we would again emphasise that the really predisposing moment in the case of pneumonia is to be found, not in those incidental and temporary impairments of resisting power which may occur in connexion with mining work, but in that abiding defect of resisting power which is normal to the native. We have here clearly a fact which dictates

recourse to inoculation, and which indicates that a very important place in our scheme of operations ought to be assigned to this measure.

(c) Our recommendations in connexion with inoculation are as follows:—

We recommend that prophylactic inoculation should, except only in the case where a mass-experiment is being undertaken, be applied as a routine measure to every native on recruitment. In the light of the results furnished by Mass-experiment No. 5 (Table XVII.), we suggest that a dose of 1000 millions of pneumococci cultivated upon glucose blood broth might appropriately be employed as the ordinary prophylactic dose.

We further recommend that the natives should be reinoculated after the expiration of four months, and that here again a dose of 1000 millions of pneumococci should be employed.

We would not for the present advise any general application of therapeutic inoculation. We would, however, urgently recommend that it should be made the subject of further investigation.

We regard the continued prosecution of research in connexion with inoculation as essential to the attainment of the best results.

We recommend that such research should comprise, on the one hand, the institution of properly controlled mass-experiments, and, on the other hand, the systematic measurement of the protective substances produced in response to inoculation. In such measurements we suggest that the method for measuring the phagocyto-bactericidal power of the blood which is described in this report, or some modification of that method, should be utilised.

In connexion with prophylactic inoculation, the task of research should be to obtain confirmation of the conclusion that we have in 1000 millions the optimum dose for prophylactic purposes. It would also be well to make certain that reinoculation after a period of four months is really required.

In connexion with therapeutic inoculation, the first task of research should, we think, be to institute a mass-experiment in which one large dose of vaccine should be given to the patient at the outset of his pneumonia attack. We suggest that a dose of 500 millions might be tentatively employed in such an experiment, and we think that in such an experiment every alternate patient should be taken for a control.

In concluding this report we desire again to express our obligations to Dr. G. A. Turner for unwearied assistance in connexion with the inoculations which we carried out on the Rand, and to Dr. F. C. Lister, Dr. A. R. Friel, and Mr. G. Friel for valuable help in our laboratory work. We desire also to thank Mr. P. Ross Frames, chairman of the Research Committee and managing director of the Premier Mine, for the helpful assistance he afforded us in both of these capacities. And to Dr. J. C. A. Rigby and to Mr. H. P. Sheridan we owe a very special debt of thanks for their eminently successful achievement—the mass-experiment carried out on the Premier Mine.

Finally, the author of this report desires to express to Dr. W. Parry Morgan, who took independent charge of the inoculation work after March, 1912, his grateful acknowledgments for his initiative and forethought in planning Mass-experiments Nos. 3, 4, and 5, and for the solicitude with which he carried these out. In connexion with our work acknowledgments are also due to the excellent and conscientious labours of Mr. O. Slawkowsky, our chief laboratory assistant, and of Mr. P. Hardwick, our statistical clerk.

¹⁰ It may be explained that "change-houses" are sheds in which the native is compelled to change clothes before he emerges from the mine into the open air.