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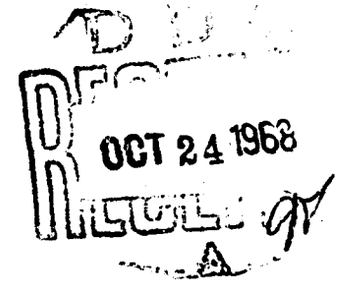

DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

[redacted]
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(In full)
By:
L. Lulich

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Faibich, M.M. and Tamarina, T.S. (Scientific Research Institute of Epidemiology and Hygiene of the Red Army)

TULIAREMIINAIA SUKHAIA ZHIVAIA VAKTSINA NIIEG KRASNOI ARMII
Soobshchenie II

DRY LIVING TULAREMIA VACCINE OF NIIEG OF THE RED ARMY
Report II

ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII I IMMUNOBIOLOGII, 10:23-27. 1946.

(In Russian)

DRY LIVING TULAREMIA VACCINE OF NIIEG OF THE RED ARMY
Report II

The purpose of this report is the exposition of the results of study of the reactivity and immunogenic properties of the dry living tularemia vaccine of NIIEG which was prepared by the method of desiccation in a high vacuum of the frozen, in the saccharose-agar-gelatin medium, cultures of the vaccinal strains Ondatra IV and No. 15 which were proposed by Gaiskii.

The dry living tularemia vaccine (equally as the cultures of the original strains Ondatra IV and No. 15), in doses proposed for the vaccination of men (12,500,000-25,000,000 microbes) and even doeses 10 times greater, causes in guinea pigs only a weakly marked reaction: locally, a small inflammatory infiltrate is registered; in some cases - an enlargement of the regional lymphatic glands and a rise in temperature for 1-2 days. The safety of these doses of the vaccine is demonstrated also by the data of histological examinations (Chalisov) which have established that in guinea pigs emerge changes, of productive benign character, in lymphatic glands and internal organs. More massive doses of the dry living vaccine, reaching 0.5 - 1 billion, cause a more intensive reaction but the loss of animals is nevertheless not observed. The lethal dose of the dry vaccine from the strain No. 15 is 3 billion, and considerably greater from the strain Ondatra IV.

The dry living tularemia vaccine, as also the cultures from the initial

strains, proved more virulent for white mice than for guinea pigs. This is explained by the greater sensitivity of the former toward the tularemia toxin. How. er, despite this the white mice withstand rather considerable doses of the living vaccine. The strain Ondatra IV turned out to be more virulent for mice than the strain No. 15. Living vaccine from the strain No. 15 in doses up to 1,000 microbes does not kill white mice, and an overwhelving majority of these animals endure also doses reaching up to 10,000,000 microbes. But the vaccine from the strain Ondatra IV in quantity of up to 1,000 microbes kill 15-20% of white mice, while the doses exceeding 1,000 microbes are fatal for 50% of mice.

Thus the experiment on white mice and guinea pigs has shown that the strains from which the dry living tularemia vaccine of NIIEG has been and is being prepared are not completely avirulent for small laboratory animals: the strain Ondatra IV is virtually avirulent for guinea pigs and weakly virulent for white mice, while the strain No. 15 is, conversely, more virulent for guinea pigs and less virulent for white mice. Thus both strains possess in one degree or another a "residual" virolence.

It should be noted that both the desiccation of the cultures of vaccinal strains for the obtaining of dry living vaccine and the addition of agar or other substances (entering into composition of the semiliquid medium) to the media did not modify their reactivity.).

The data of comparative study of the dry living tularemia vaccine on guinea pigs (both from the agar and the semiliquid medium), which was prepared from the strain No. 15 or Ondatra IV, show that it posseses a high immunogenicity but that immunogenic properties of both strains are different. Single subcutaneous vaccination with the dry vaccine from the strain Ondatra IV in does of 125,000 microbes and more, or with the dry vaccine from the strain No. 15 in does of 6,000 microbes and more, protects the guinea pigs in 100% of cases from their subsequent infection with 1,000 absolutely fatal doses of virulent culture of tularemia bacilli. The high immunogenicity of thevaccinal preparation is confirmed also

by its ability to furnish 100% protection of guinea pigs, vaccinated subcutaneously, from the subsequent infection through the lungs with the pulverized suspension of virulent culture which causes death of all unvaccinated animals. In the vaccinated animals, after their infection with 1,000 fatal doses, was ascertained neither a rise in temperature nor loss of weight.

The high immunogenicity of the dry tularemia vaccine from the strain Ondatra IV and No. 15 has been established also on white mice - animals very susceptible to tularemia. Single subcutaneous vaccination with the dry vaccine from the strain No. 15 in dose of 1000 microbes, or with the vaccine from the strain Ondatra IV in dose of 15,000 microbes, protects white mice 100% from 1,000 fatal doses in subcutaneous infection, and 65% in pulmonary infection with the virulent culture of tularemia bacilli.

The dry living tularemia vaccine, prepared on saccharose-agar-gelatin medium and kept in hermetically sealed ampules with vacuum, remains immunogenic for a long time. Thus, the dry vaccine, kept at 18° for 270 days, at 26° for 75 days, or at 2-4° for 1.5 years, after single subcutaneous vaccination in doses from 10 to 25 million microbes, protects 95-100% of guinea pigs and white mice from the subsequent subcutaneous infection with 1,000-2,000 fatal doses of the virulent culture. The data on the stability of the dry living vaccine are corroborated also by the fact that this vaccine, prepared from the culture grown on semiliquid medium, after 30 days of storage at 26° did not modify its original minimum immunizing dose for guinea pigs.

The dry living vaccine, kept at 18° in sealed ampules but with broken vacuum, after 60 days did not develop immunity in white mice apparently as a result of the absence by this time of living microbes in it.

Attention is drawn by the following fact: the dry living tularemia vaccine, as also the native suspensions of the cultures of the strain Ondatra IV and No. 15, only in the doses capable of producing a reaction, developed unsusceptibility in guinea pigs in 90-100% of cases, inasmuch as for the development of immunity

necessary is the penetration into the organism of such quantity of living microbes of the vaccine as are capable of "acclimatizing" themselves, multiplying in the place of introduction, and then invading the organism, producing on its part the appropriate reaction. As a result of this reaction (under the conditions, of course, of high antigenicity of the strains), the unsusceptibility develops in the vaccinated animals. As the experiment has shown, in orderto develop immunity of the maximum intensity (securing not less than 90" survivability of animals)it is required to introduce into white mice not less than 10 microbes of the fresh culture of the strain No. 15, and not more than 1,000 microbes of the strain Ondatra IV; and into guinea pigs - respectively, not less than 1,000 and not less than 10,000 microbes. Cultures of the indicated microbes in smaller doses develop immunity in not more than 50% of cases. (Gaiskii's date, pointing to the circumstance that the attenuated strains in nimimum doses (1,2 or 5 microbes) protect all mice and guinea pigs from large doses of the virulent culture, have not been confirmed in or experiments.)

The study on guinea pigs of the problem of the periods of development of immunity, which is of great practical significance, has shown that after introduction of 12.5 million microbes of the dry vaccine from the strain No. 15 the immunity begins to be detected already on the 3rd day (a portion of the animals survive) and reaches the maximum intensity in 15 days (all animals survive). After the introduction of 25 million dry vaccine from the strain Ondatra IV the immunity emerges somewhat later - on the 8th day, but it reaches the maximum intensity also in 15 days. Negative phase has not been observed in the animals vaccinated with the living vaccine.

The study of immunogenic properties of the dry living vaccine kept for almost 2 years has shown that it can be preserved for 270 days at 15°, and for over 1.5 years at 2-6°. These investigations confirmed once again that the strain

No. 15 in comparison with the strain Ondatra IV, has more marked immunogenic properties.

The study of the dry living tularemia vaccine on men - initially on 52 volunteers who received the vaccine in doses ranging from 7.5 to 250 million microbes (Kopylov, Faibich, Nikolaev, Saltykov), and then on more than 30,000 men who received the vaccine in doses ranging from 12.5 to 50 million (Faibich, Zlatkovskii, Belenkov and Saltykov) - has shown that all the above-described variants of this vaccine are endured by men relatively easily, without a prolonged reaction or complications. To the subcutaneous introduction of even large doses of the vaccine (from 100 to 250 million microbes) the men reacted with a brief local and general reaction which ran benignly. Moreover, reaction on the part of the regional glands was not observed in all cases. In doses of up to 50 million the vaccine is endured by men entirely easily and it causes mainly a mild local reaction and in rare cases - a weak reaction on the part of the regional lymphatic glands, and still less frequently - a temperature reaction.

The persons who have had tularemia react to the introduction of the living vaccine considerably more strongly, which must be explained by the presence in them of increased sensitivity.

However, the doses which do not exceed 25 million microbes do not cause even in those who have had the illness a sharply pronounced reaction which disrupts their work capacity. Thus, a brief rise in temperature above 38°was observed in 1.4% out of the 1,000 men among whom there were 20% of those who have had the illness.

The results of the study of the vaccine from different strains on men, as also in experiment, have shown that the vaccine from the strain No. 15, in comparison with the vaccine from the strain Ondatra IV, has more pronounced allergenic and antigenic properties even after one month it causes in all the inoculated men a positive agglutination reaction and the allergy condition, whereas the vaccine from the strain Ondatra IV, one month after the inoculation, causes the agglutination

reaction in only 35%, and the allergy reaction in 83% of cases. The allergy condition, increased as a result of vaccination, in preserved in all those inoculated for one year (observation period, Kopylov, Faibich, Nikolaev and Saltykov). This fact is of vast significance and is a convincing proof the high effectiveness of the vaccine.

After introduction into men of 12.5 million microbes of the dry living vaccine kept for one year, the intracutaneous allergy reaction became positive after 6 days in 50% of the inoculated, after 10 days - in 77.3% and after 15 days - in 100% of the inoculated (Zlatkovskii).

These data on the periods of appearance of the intracutaneous allergy reaction in men, inoculated with the dry vaccine, concur with the periods of appearance of immunity in guinea pigs vaccinated with it, as well as with the periods, established by Drobinskii and Belenkov, of appearance of the intracutaneous reaction in men who contracted tularemia spontaneously. These data attest to the high effectiveness of the dry vaccine and together with it furnish the basis to assume that it, in the dose of 12.5 million microbes, after keeping one one year (period of observation), causes in men an immunobiological reorganization analogous to that developing after the endured spontaneous ailing which develops, as is known, a long immunity.

Thus, the cited results of the study on men of the reactivity and immunobiological activity of the dry living vaccine give us the right to recommend this vaccine, in doses of up to 25 million microbes, for vaccination of men in epidemic foci without a preliminary separation of men who have had tularemia. The doses of the dry vaccine from the strain No. 15 ranging from 10 to 25 million are fully effective and are easily endured even by persons who have had the illness. This is extremely important in practical respect, for in mass vaccination in regions with the presence of a large number of those who have had the illness the separation of the latter is not always possible.

On the basis of the date studied in the present investigation, it must be concluded that for vaccination of men the most suitable is the vaccine from the

strain No. 15. At the same time, it must be kept in mind that, inasmuch as the vaccinal strains are not identical in antigenic and immunogenic respects, the preparation of a plyvalent dry vaccine from several vaccinal strains of tularemia is expedient. This brings forth the necessity of finding new effective strains of the type of strain No. 15. As a result of the study of a large number of cultures of tularemia bacilli with spontaneously attenuated virulence, we have at the present time found two such strains. One of these, designated No. 10, was obtained in 1944 from the Saratov Institute under the name "Bulukhta", with unstudied immunogenic and virulent properties. This strain is less reactive for guinea pigs and white mice than the strain No. 15, but the living vaccine from it has high immunogenic properties and protects all guinea pigs (vaccinated with 10,000 microbes) from the subsequent infection under the skin (1,000 fatal does) and through the lungs. White mice, vaccinated with 1,000 microbes of the vaccine from the strain No. 10, withstand, without the symptoms of the illness, 1,000 fatal doses of the virulent culture introduced under the skin. These data of experimental study give us the basis to embark upon the study of the strain No. 10 on men.

CONCLUSIONS

1. The dry living tularemia vaccine of NIIEG, prepared from vaccinal strains, is capable of preserving its activity for a long time (up to 1.5-2 years).

2. Of the two strains proposed by Gaiskii - Ondatra IV and No. 15 - the most suitable for vaccination of men is the strain No. 15.

3. The dry livingttularemia vaccine from the strain No. 15 Possesses high immunogenic properties both for laboratory animals (guinea pigs and white mice) and for men.

4. The safety of the dry living tularemia vaccine has been demonstrated on experimental animals and on a large number of men (over 30,000 men have been inoculated).

5. For vaccination of men it is recommended that the dry living tularemia vaccine be employed once in doses ranging from 10 to 25 million microbes.

6. The new strain No. 10 which we found was high immunogenic properties and can apparently be, after a preliminary testing on men, employed for preparation of a polyvaient dry living tularemia vaccine.

This paper gives some detail on Animal & human response to the Dry vaccine and its components. Procedures and destinctions made in the field of genetics are reminiscent of 1920 bacteriology. This situation is evident throughout the work, but the intent and practical value of the vaccine is nevertheless impressive.