

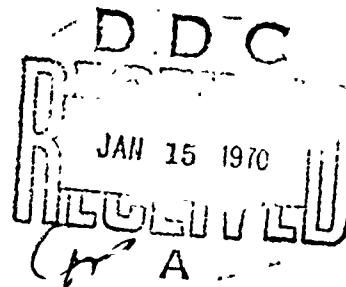
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SIMULTANEOUS IMMUNIZATION OF HUMANS WITH LIVE BRUCELLOSIS
AND Q FEVER VACCINES

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Experiments on guinea pigs showed that two live vaccines -
brucellosis and Q fever when applied subcutaneously and epidermally -
are compatible and confer good immunity, (Knyazeva, 1965, 1966).
Somewhat earlier Silich et al. (1962) obtained satisfactory results
from simultaneous immunization of humans with live brucellosis
and killed Q fever vaccines.

The purpose of this work was to study the reactivity and
immunologic effectiveness of simultaneous vaccination of humans
with brucellosis and Q fever vaccines and to determine the most
effect way of administering them.

Our subjects were ~~persons~~ directly exposed to the danger of
infection - meat packers, ~~and~~ dairy workers, and students of agricultural
and veterinary schools. Apparently healthy males and females
14 to 50 years of age were inoculated. They were first examined for
immunologic reactions to brucellosis and Q fever. In studying
the immunologic effectiveness of the inoculations, we took into
account only the data on ~~those~~ ^{those} ~~persons~~ persons in whom the results
of all the reactions were negative prior to vaccination. A total
of 642 persons ~~received~~ ^{received} the two vaccines.

Three methods of vaccination were used: (i) subcutaneous, with associated brucellosis-Q fever vaccine; (ii) combined, when Q fever vaccine was injected subcutaneously along with epidermal application of brucellosis vaccine; (iii) epidermal, when both vaccines were ~~applied~~ applied to different portions of the skin.

The materials were the experimental series of Q fever vaccine prepared from the C. burneti M-44 strain and the ~~subcutaneous~~ subcutaneous brucellosis vaccine produced by the Gamaleya Institute of Epidemiology and Microbiology. The associated Q fever-brucellosis vaccine was prepared just before administration from brucellosis and Q fever vaccines by mixing the two. ~~With~~ ^{With} combined and epidermal vaccination, we used brucellosis epidermal vaccine made by the Kashintsev ~~Biofactory~~ ^{Biofactory} (series 694, 115, and 1158) in a dose of $6 \cdot 10^9 - 8 \cdot 10^9$ live brucellas. With subcutaneous vaccination, one vaccinal dose contained $4 \cdot 10^8 - 5 \cdot 10^8$ live brucellas, while a dose of Q fever vaccine contained $10^5 - 10^6$ minimal infectious doses for an embryo (MIDE) in a volume of 0.5 ml. With epidermal vaccination, Q fever vaccine was administered to one group in a dose of $10^7 - 10^8$ MIDE; to another, in a dose of $5 \cdot 10^7 - 5 \cdot 10^8$ MIDE. Both vaccines were applied separately to different ~~arms~~ arms, to ~~the~~ forearm skin, 2 drops on each. Six scratches were made through the drops, after which the vaccine was rubbed in and then allowed to dry completely.

One hundred persons received the associated Q-fever-brucellosis vaccine subcutaneously in the subscapular ~~region~~ or brachial region. These persons were observed ~~on days~~ 2-3 and 6-7 days after vaccination by examining the vaccination site and asking questions. A local reaction in the form of an infiltrate, hyperemia, and tenderness was noted in 50. A systemic reaction occurred, as a rule, two or three days after vaccination and was manifested by malaise and headaches. A few complained of chills and rheumatic pain in the joints. Of 92 vaccinates under observation, 48 presented a variety of complaints. Nineteen experienced a brief elevation of temperature to $37.5-38.5^{\circ}$; 5 of them were unable to work. Thus, subcutaneous ~~vaccine~~ inoculation of the associated vaccine proved to be reactive, which led us to resort to other methods.

It is a known fact that epidermal vaccination against brucellosis ~~epidermal vaccination~~ does not provoke any significant reaction ^{in individuals}. We deemed it worthwhile, therefore, to determine the reactivity and immunologic effectiveness of vaccination combining epidermal inoculation of brucellosis with subcutaneous ~~or~~ epidermal inoculation of Q fever vaccine. A total of 155 persons ~~were~~ received the epidermal brucellosis and subcutaneous Q fever vaccines. Of 102 persons observed in this group, only 7 presented complaints of malaise, headache, weakness, etc. 2-3 days after inoculation. All were able to continue working.

A group of 589 persons was inoculated by scarification.

Both vaccines were applied separately through scratches on ~~the~~ ^{forearm} the ~~forearm~~. Of these, 243 received $10^7 - 10^8$ MIDE of Q fever vaccine ~~and~~ and 146 received $5 \cdot 10^7 - 5 \cdot 10^8$ MIDE. The reaction to the inoculation was ascertained by questioning the individuals and by examining the ~~inoculation~~ site at intervals ranging from the first to the 10th-12th days after inoculation. In this group 202 persons were kept under observation. Two of these presented complaints of weakness and malaise on the second day after inoculation, but all the rest retained their sense of well-being. The local reaction both to the brucellosis and to the Q fever vaccine was expressed in hyperemia and slight edema along the scratches and, in some cases, small nodules. The reaction to the brucellosis vaccine appeared the first day after inoculation, but it subsided 7-10 days later. The reaction to the Q fever vaccine appeared only on the 3rd day after inoculation, was most pronounced on the 4th and 5th days, and then gradually subsided. We were unable to detect any difference ~~between~~ between the $10^7 - 10^8$ and $5 \cdot 10^7 - 5 \cdot 10^8$ MIDE with respect to the time of appearance, subsidence, and intensity of the skin reaction.

Immunity was ~~investigated~~^{evaluated} in the vaccinates at various periods using the complement-fixation test with Q fever antigen, the agglutination, Wright's, ~~and~~ Huddleson's, ~~and~~ and Burnet's tests.

Examination of those inoculated subcutaneously with the associated vaccine ~~3-3½~~^{after} months revealed ~~a~~ satisfactory ~~immunity to both antigens~~ immunity to both antigens. Of 35 sera, the ~~reaction in~~ Wright's test was positive in 35 with a mean reaction titer of 1:214. In the complement-fixation test with Q fever antigen, the reaction was positive in 35 (80%) of the 43 persons examined, the mean titer being 1:36.

Table 1 (serologic reactions) contain ~~the~~ data on the immunologic effectiveness of the combined method with ~~epidermal~~ injection of brucellosis vaccine. Tables 2 and 3 present the results of examining the groups inoculated by the epidermal method using different doses of Q fever vaccine. It follows from these data that immunity to both vaccines was satisfactory in all three groups.

A comparison of the data shows that the largest number of persons who reacted positively in the CFT, the highest titers and longest persistence were in the group that received $5 \cdot 10^7 - 5 \cdot 10^8$ MIDE of the Q fever vaccine. This is in full agreement with Genig's data (1965) obtained ~~by~~^{after} epidermal application of vaccine from strain M-44. More than 90% of this group exhibited immunity to both antigens

a month later. After 5 months the number of those who reacted positively and the mean antibody titers remained on a high level, showing that the vaccinal process developed vigorously at this time. Ten months later the indices of the serologic reactions decreased, but allergic reconstruction persisted in most of the vaccinates (88%).

Table 1

Results of Seroallergic ^y ~~Tests~~ ^(Tests) of Persons Inoculated Simultaneously Against Brucellosis and Q Fever by Epidermal Application of Brucellosis Vaccine and Subcutaneous Injection of Q Fever Vaccine

- 1 - Time of examination after vaccination (in months)
 - 2 - Brucellosis + Q fever vaccines ($10^5 - 10^6$ MIDE)
 - 3 - complement-fixation test with ~~antigen~~ Q fever antigen
 - 4 - number of persons examined
 - 5 - with positive reaction
 - 6 - mean titer ~~Wright's test~~
~~antigen~~
 - 7 - Wright's test
 - 8 - Huddleson's test
 - 9 - Burnet's test
 - 10 - Q fever vaccine ($10^5 - 10^6$ MIDE) (control group)
 - ~~antigen~~
-

Table 2

Results of Seroallergy Tests of Persons Inoculated ~~Simultaneously~~
Simultaneously with Epidermal Brucellosis and Q Fever Vaccines
($10^7 - 10^8$ MIDE) and Corresponding Monovalent Vaccines

- 1 - Group of persons vaccinated
 - 2 - Time of examination after vaccination (in months)
 - 3 - Result
 - 4 - complement-fixation test with Q fever antigen
 - 5 - number of persons examined
 - 6 - with positive reaction
 - 7 - mean titer
 - 8 - Wright's test
 - 9 - Huddleson's test
 - 10 - Burnet's test
 - 11 - Mixed vaccination
 - 12 - Q fever
 - 13 - Brucellosis
 - 14 - Control - inoculation with monovalent vaccines
-

Table 3

Results of Seroallergy Tests of Persons Inoculated Simultaneously
with Epidermal Brucellosis and Q Fever Vaccines ($5 \cdot 10^7 - 5 \cdot 10^8$ MIDE)

- 1 - Time of examination after vaccination (in months)
- 2 - Result of vaccination
- 3 - brucellosis + Q fever vaccines
- 4 - complement-fixation test with Q fever antigen
- 5 - number of persons examined; 6 - with positive reaction; 7 - mean titer
- 8 - Wright's test
- 9 - Huddleson's test
- 10 - Burnet's test
- 11 - control - complement-fixation test with inoculation of Q fever vaccine

Thus, the ^(results were) most satisfactory ^(among) ~~results were obtained among~~ the
^(epidermally) persons ~~examined with~~ inoculated with both vaccines separately,
with Q vaccine used in a dose of $5 \cdot 10^7 - 5 \cdot 10^8$ MIDE.

A comparison of the number of those who reacted positively
and the titers of the serologic reactions in those ^(receiving) ~~examined with~~
the two vaccines with the control individuals inoculated with the
corresponding monovalent vaccines (our own data [Tables 1-3] and
the literature data) failed to reveal any evidence that the antigens
inhibited each other. The lack of competition between the vaccines
was also confirmed by analyzing the titers of the CFT and Wright's
test. If the results of the serologic reactions are distributed in
groups according to the height of the titers, the larger values of

the mean titers of the CFT will correspond to the high titers of Wright's test, and vice versa. This relationship was ^{very} clearly manifested 3 months after vaccination when the number of Wright test positives reached a peak (Table 4).

Table 4

Relationship Between the Results of Wright's ^{Test} and ^{the} Complement-Fixation Test with Q Fever Antigen in Persons Inoculated with the Two Vaccines 3 Months After Vaccination

- 1 - Number of sera
 - 2 - Result of Wright's test
 - 3 - Mean titer of the complement-fixation test with Q fever antigen
 - 4 - Negative
 - 5 - 1:800 and higher
 - 6 - *The results were positive with all these sera in Huddleson's test
-

The results of our study of the immune response in persons inoculated with live brucellosis and Q fever vaccines suggest that the simultaneous skin application of these vaccines can ~~have~~ ^{have} produce a definite epidemiologic effect.

Conclusions

1. The simultaneous inoculation of brucellosis and Q fever vaccines subcutaneously, epidermally, and by the combined method (subcutaneous injection of Q fever vaccine and epidermal application of brucellosis vaccine) produced immunity to both vaccines.

~~the~~ Q fever vaccine used in an ~~amount~~ equal to

2. ~~the~~ Epidermal application of the two vaccines with $5 \cdot 10^7 - 5 \cdot 10^8$

MIDE produced the optimal immunologic effect along with insignificant local and systemic reactions.

3. Our data justify the recommendation that live brucellosis

and Q fever vaccines be applied to the skin simultaneously *for practical immunization purposes* and that their epidemiologic effectiveness of the method be studied.

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