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TRIALS WITH MEASLES VACCINE IN A VIRGIN POPULATION

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It is commonly supposed that populations experiencing a disease that is new to them may be affected more severely than populations that have had several generations in which to develop or to be selected for resistance. A classic example of this is the effect measles has had in virgin-soil populations of Oceania and the New World. Unfortunately, virgin-soil epidemics, by their very nature, occur under circumstances that are not comparable to those of experienced communities and meaningful data on these epidemics are practically non-existent.

If, however, the American Indian is more susceptible to measles than other races, it is, on the one hand, more important to immunize him and, on the other, possibly more dangerous to administer standard live vaccines. It has been the primary purpose of this study to measure the reactions of a virgin-soil Indian population so as to estimate the magnitude of this problem and to find the best path between the two hazards. Secondary objectives have been: (1) Determination of stability of antibody in the absence of reexposure in a previously vaccinated tribe; (2) Measurement of the total burden of viral infection in a tribe before it becomes exposed to the diseases of civilization; and (3) Determination of blood groups in a relatively "pure blooded" tribe.

Locale

The study was carried out in the Xikrin Indians, a tribe of 121 Cayapos living 500 kilometers southeast of Belém. They were first pacified in 1954, but, except for a brief period around 1962, have remained isolated in the forest and have retained most of their own culture.

For this study, the tribes were divided into two groups approximately balanced for age and sex (Table 1). The age distribution pattern showed a

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deficiency of older children and very few older persons. In general, they were in good health, but enlarged spleens, presumably due to malaria were found frequently, and many gave positive tuberculin reactions. Other conditions - heart murmurs, post encephalitic paralysis, poliomyelitis-like limb weakening, and cataracts were found in a few instances. Respiratory disease was a problem during the period of study.

Measles Vaccine Reactions

Members of one-half of the tribe were given Schwarz further-attenuated measles vaccine intramuscularly on day zero. Temperature measurements were taken at the arm pit every afternoon on the whole tribe. Aspirin was given to anyone with a temperature over 39.4°. On day 13 vaccine was given to the second group. Temperature recordings were suspended for six days and then resumed until the 27th day. Serum samples were collected on days 1 and 27 and citrated bloods for genetic studies on days 14 and 27. Only three adult men, all of whom had worked for extended periods with the Caboclos, had serological evidence of past measles infection. These persons have been removed from further consideration. The highest temperature recorded during the second post-vaccinal week - the usual time of measles vaccine reaction - have been compared in each group with the highest recorded temperatures in the other half of the tribe. Results are given in Table 3.

The average temperatures were similar to those observed in a previous study in the Tiriyo Indians of the northern Amazon (Am J Epid 89, 168) and were considerably higher than in a standardized series conducted by the WHO even though the latter temperatures were recorded rectally. The values observed in the Xikrin control groups were, however, higher than in the other studies so that the observed elevations were somewhat less than in Tiriyo.

The Tiriyo and Xikrin have similar age distributions but age-related differences in responsiveness complicate comparisons with other groups. Adjustments have been made to normalize data to what would be expected if all subjects were five years old and several studies are

compared on this basis in Table 4. We believe that this demonstrates that virgin-soil Amerind populations do react more strongly to measles vaccine and suggests that they would also be more severely affected by wild measles.

The magnitude of this difference is such that the Schwarz or Edmonston vaccine with gamma globulin give approximately the same effect as Edmonston alone in other populations. It is our considered opinion that use of the less attenuated vaccines in these populations without gamma globulin entails a risk for which safety checks in other populations are not entirely relevant.

The responsiveness of the American Indian to measles virus may be genetically determined or it may be contingent on synergistic effects of other diseases. In this study we had an opportunity to examine some of the more important complicating factors. In Tiriyo, a para-influenza epidemic concurrent with vaccine reaction in one group was associated with high fevers. In Xikrin, an upper respiratory epidemic also occurred, when the second group was incubating vaccine virus. Control temperatures in children were higher at this time but there was no corresponding effect on the temperatures in vaccinees. Bronchitis and pneumonia may, however, have resulted from the combined infection as there was a temporal association here (Table 5).

Much of the fever in the control groups occurred in the individuals with enlarged spleens. The study was conducted during the rainy season and Falciparum tropozoites were found in four blood smears. Complete screening by examination of smears was frustrated by difficulty in preserving the specimens. The possibility suggested by Neel et al. that a synergistic relationship between malaria and the vaccine virus might account for the high fevers was examined. However, the effect of these two diseases on fever was less than additive (Table 6). There was no significant pattern of relationship between tuberculin sensitivity and fever (Table 6).

Serological responses of the Xikrin to the vaccine were entirely normal, with antibody appearing in at least the usual titer two to four weeks after vaccination. Serum samples collected from the Tiriyo showed that they had maintained normal measles antibody titers over the period of three and

one-half years since they were vaccinated, although there had been no conversions to immunity in unvaccinated persons and thus no exposure of the vaccinees.

Infectious Disease Serology

The results of various serological tests are given in Table 7. Neutralization tests against a wide selection of arboviruses have also been carried out but not yet analyzed. The most striking aspect of this table is the paucity of positive reactions with the myxo- and para-myxoviruses. Generally when only a few positive specimens were found, they were from the younger adults who had travelled the most widely. Measles, rubella, and the influenzas seem never to have reached the tribe itself.

No one under the age of 17 had Type 1 or 3 para-influenza titers greater than ten. These viruses may have been epidemic in the tribe some years back but not recently.

Type II poliovirus antibody was found in all age groups, but there were no significant Type I titers under age 16 and no significant Type III titers under seven. These ages did not, however, mark a sharp cut-off as there were numerous negative specimens in older age groups. This is the same pattern as was observed in the classic study by Paul et al. on Alaskan Eskimo, but modern tests for antibody are considerably more sensitive, and either there must have been a considerable decline of titer from initial levels or some persons must have escaped the epidemic even in this close-knit community.

In contrast to these systems, the prevalence of reactions to herpes group viruses and to Australian antigen were generally more common than in other populations. We believe that these viruses had the ability to remain endemic even in this small isolated population. These may be the only agents studied that did not have to be introduced from outside.

Blood Groups

Blood group reactions of the Xikrin have been determined by J.V. Neel

and F. M. Salzano, and have been integrated with studies on other Cayapo tribes by Dr. Salzano. Types A_1 and B were absent altogether. R^2, R^o and r genes were very rare. The Di^a gene had a frequency of 27%. There were no unusual antigens and the Xikrin pattern fits well with the other Cayapo groups, being especially close to the Kuben-Kran-Kegn. We hope that this study will be valuable in elucidating the role of genetic drift in small human populations.

Perspectives

We believe that, including this study, there is now convincing evidence that virgin-soil groups of Amerinds react to measles vaccine more strongly than do other populations. We have made some progress in eliminating non-genetic factors, particularly malaria and tuberculosis, from a putative role in this phenomenon. We believe we have demonstrated that the further-attenuated vaccine is safe, if medical support is available, but would advise against more virulent vaccines where alternatives are available.

We have demonstrated that a considerable variety of pertinent information can be derived from a well-planned but lightly financed expedition, and would urge that further expeditions be mounted to other South American tribes as they pass from the unpacified state to integration into the larger society. These further studies could be of immediate value to the Indians in determining and providing optimal immunization procedures and would be of lasting value in understanding the factors that have shaped man's heritage.

The laboratory studies related to this project have been supported by other sources but a critical component of the financing was a travel grant provided by PAHO. It was only because this grant was made available quickly and with minimal formality that we were able to seize the opportunity when it was presented.

Table 1

Distribution of Population

Approximate Age in Years	Group I		Group II		Pre-immune Not Vaccinated		Total	
	M	F	M	F	M	F	M	F
0.5-2	2	7	6	5	4		12	12
2-4	4	2	2	1			6	3
5-9	6	3	4	0			10	3
10-14	2	0	2	2			4	3
15-19	8	3	0	7			8	10
20	6	1	1	4	1		8	5
25	3	4	4	4	1	2	8	10
30	3	1	5	1	1		9	2
35	0	3	2	0			2	3
40	0	0	2	0		1	2	1
Totals	34	24	28	24	7	3	69	52

Table 2

Evidence of Malaria and Tuberculosis

Estimated Age	Palpable Spleen	Positive Tuberculin
0.5-2	2/19	1/21
2-4	2/9	0/9
5-9	5/12	5/13
10-14	5/8	4/8
15-19	9/17	9/16
20	7/13	5/9
25	11/18	6/15
30	1/10	3/8
35	2/5	3/5
60+	2/3	1/3
All ages	46/114	37/107

Table 3

Mean Maximum Axillary Temperature

	Children			Adults		
	Vaccine	Control	Diff.	Vaccine	Control	Diff.
Xikrin						
1st group	38.7	37.5	1.2	38.3	37.5	0.8
2nd group	38.8	38.0	0.8	38.1	37.5	0.6
Tiriyo						
1st group	38.7	36.9	1.8	38.4	36.7	1.7
2nd group	38.4	36.7	1.7	37.8	36.4	1.4
Iceland (rectal)				37.6	37.0	0.6
WHO 5 countries (rectal)	38.2	37.7	0.5			

Table 4

Measles Vaccine Reactions
in American Virgin-Soil Populations

Vaccine	Study	Number of Persons	Age Adjusted Difference Vacc. less Control	Difference from WHO
Edmonston B	WHO combined	212	0.92	
	Greenland under 5	89	1.35	+0.43
	Greenland all ages	294	1.44	+0.52
	Yanomama, Venezuela	21	1.8	+0.88
Edmonston B+GG	WHO combined	482	0.43	
	Chevak, Alaska	49	0.97	+0.54
	Greenland, adult	78	1.1	+0.7
	Yanomama, Venezuela	65	0.9	+0.5
Beckenham	WHO combined	289	0.69	
	Surui, Brazil	39	2.3	+1.6
Schwarz	WHO combined	372	0.43	
	Frobisher Bay, Can.	36	0.86	+0.43
	Greenland	383	0.33	-0.10
	Tiriyo, Brazil	110	1.14	+0.71
	Xikrin, Brazil	110	0.82	+0.39
All virgin soil		1274		+0.38

Table 5

Number of Individuals Developing Lower Respiratory Tract Disease after Vaccination in the Xikrin Tribe

	Day of Onset			
	0-6	7-13	14-20	21-27
58 Persons vaccinated Day 0	0	1	3	1
52 Persons vaccinated Day 13	0	2*	1	7

*Travelers arriving sick

Table 6

Associations between Mean Maximum Temperature and Splenomegaly or Tuberculin Sensitivity

	Children				Adult			
	Control		Vaccinee		Control		Vaccinee	
	Number	Temp.	Number	Temp.	Number	Temp.	Number	Temp.
Normal Spleen	38	37.6	32	38.7	33	37.1	28	38.0
Enlarged Spleen	13	38.2	14	38.7	30	37.8	32	38.3
Negative PPD	41	37.7	37	38.8	31	37.6	25	38.1
Positive PPD	10	38.1	9	38.1	26	37.5	24	38.0

Table 7

Antibodies in the Xikrin
Against Various Infectious Agents

Virus	Test	Number Tested	Number Positive	%
Measles	HA	98	3	3
Rubella	"	92	0	0
Mumps	"	82	11	13
Para-influenza 1	"	94	19	20
2	"	94	85	90
3	"	94	51	54
Influenza A_o PR 8	"	94	0	0
A_2 Taiwan	"	94	14	15
A_2 Hongkong	"	94	2	2
B Great Lakes	"	94	0	0
B Md.	"	94	0	0
Poliovirus I	Neut > 4	77	22	28
II	"	75	52	69
III	"	76	34	46
Herpes Simplex I	Neut	40	38	95
II	"	38	30	79
Cytomegalo	CF	29	18	62
Epstein-Barr	FA	95	93	98
Australia ag. or ab.	Pptn.	85	14	16
VDRL confirmed by FTA		85	16	19
Tetanus antitoxin		77	1?	