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Day-to-Day Reactogenicity of Measles-Mumps-Rubella Vaccination

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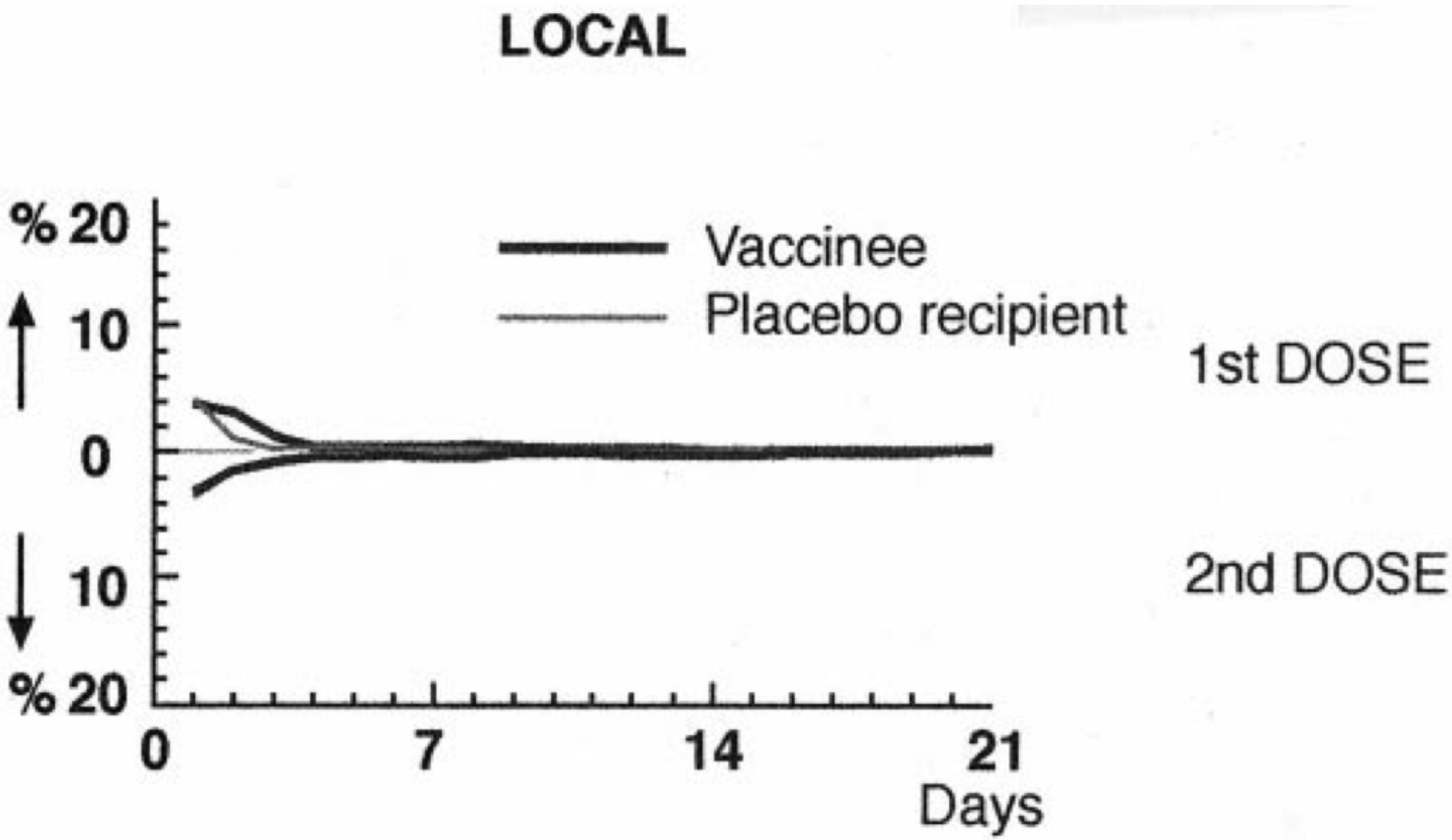
Revaccination policies adopted in many countries to control measles have raised various safety issues including those concerning the second vaccine dose.

We performed a prospective, double-blind, crossover trial among twins receiving a measles-mumps- rubella (MMR) vaccine.

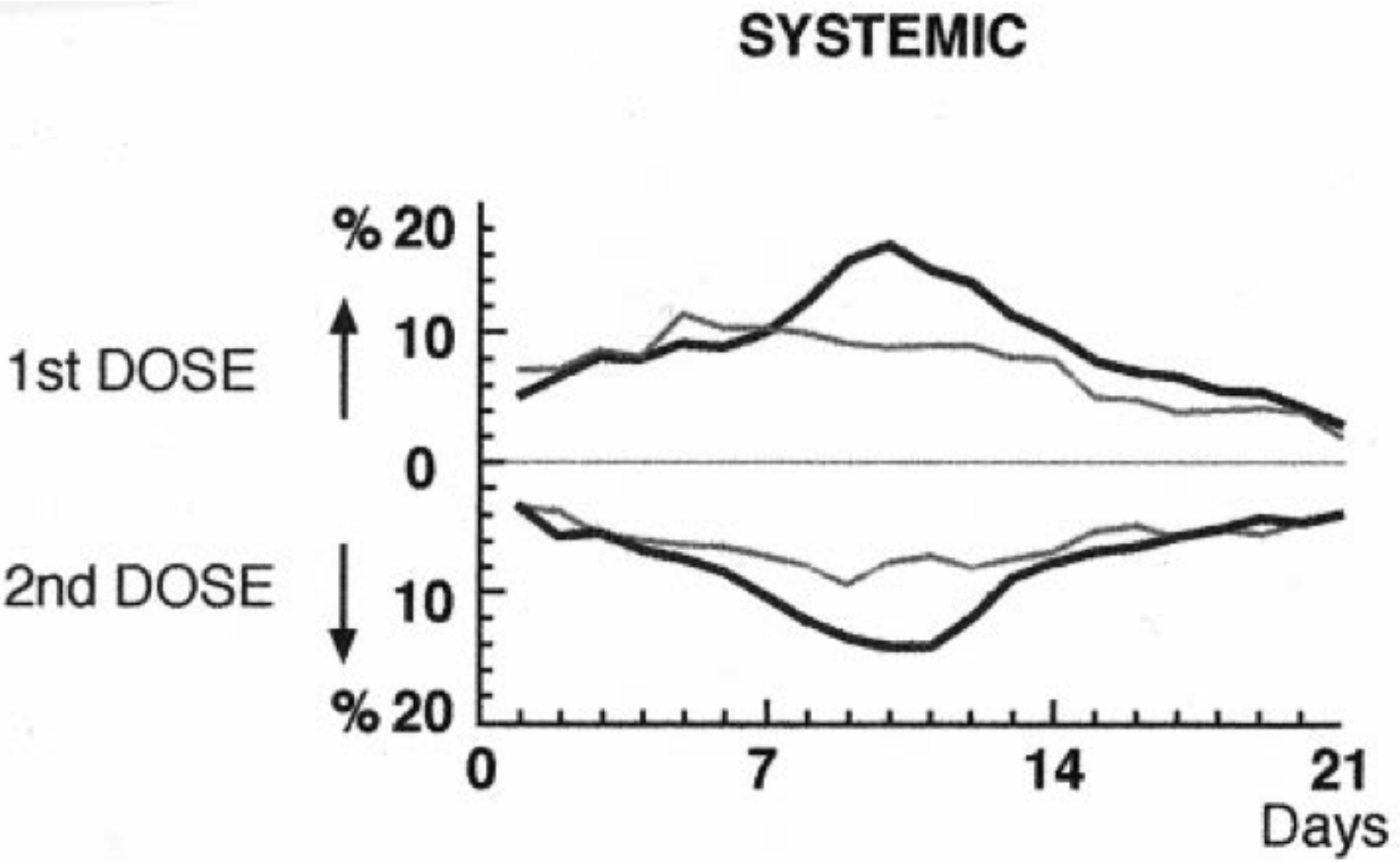
The study comprised 1162 monozygous and heterozygous twins, each of whom randomly received placebo and then vaccine, or vice versa, 3 weeks apart, at 14 to 83 months of age. Most of the oldest children had previously been vaccinated against measles, and one half of the remainder of children had had the disease.

Symptoms and signs were recorded daily on structured forms.

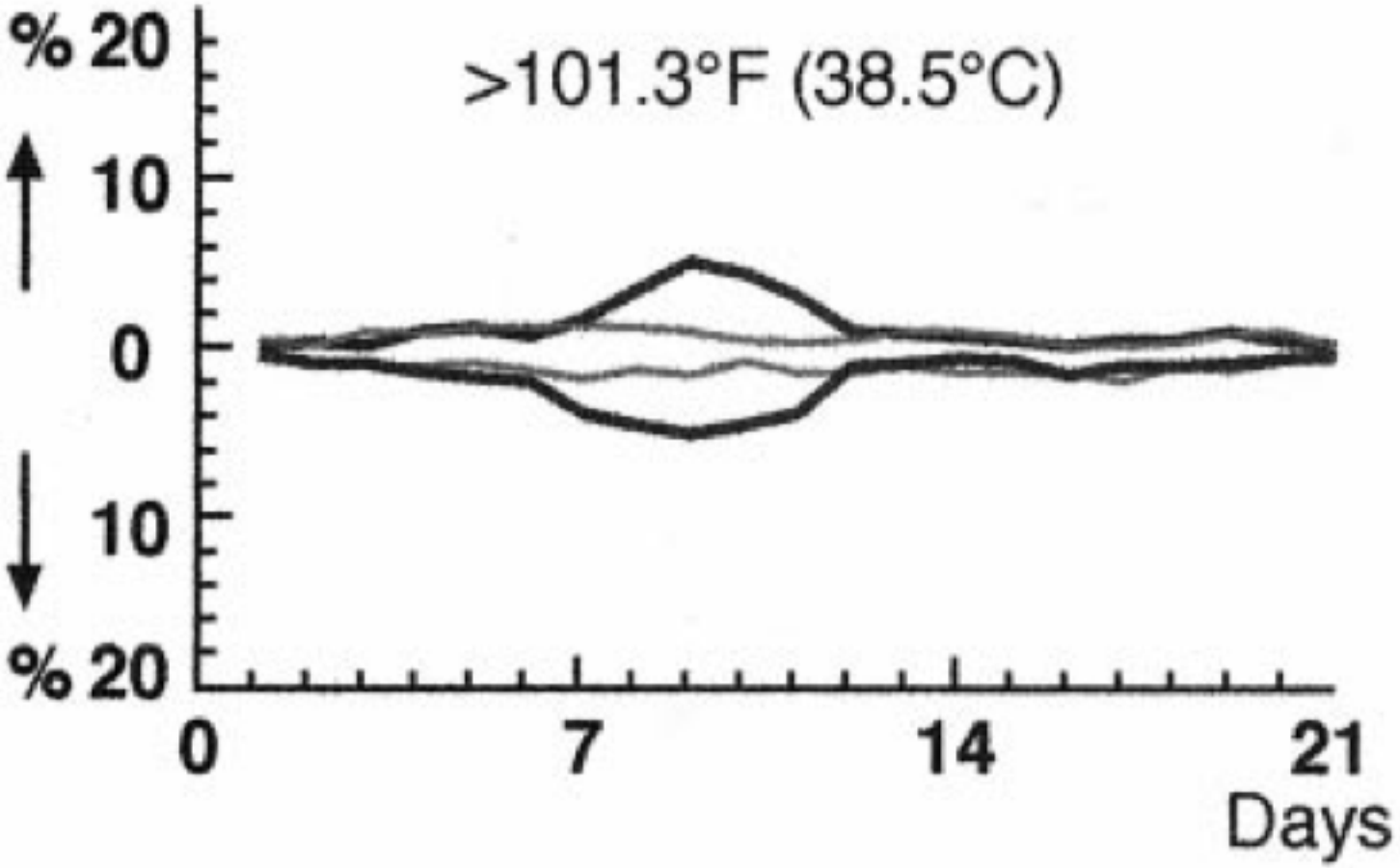


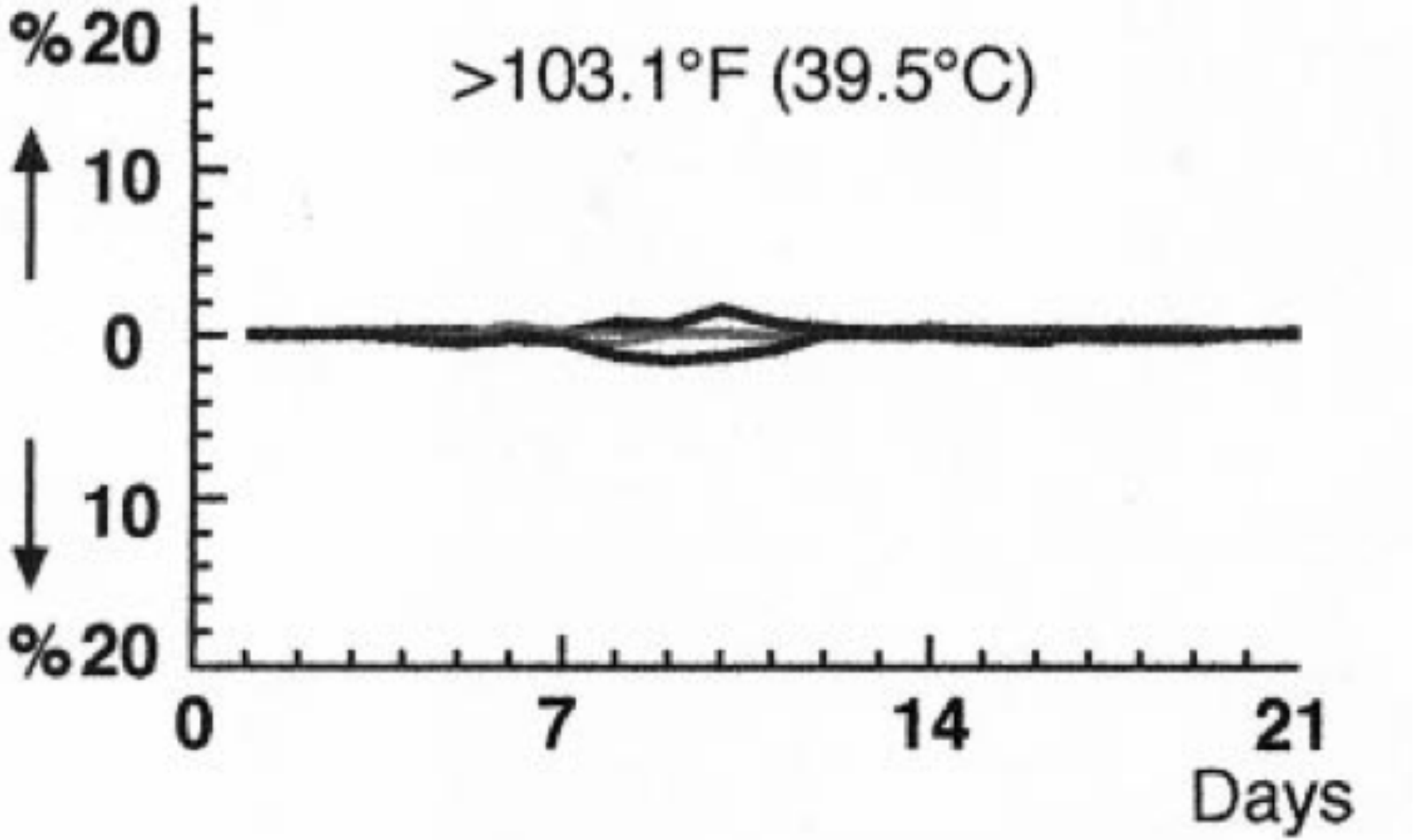
Day-to-day occurrence of other symptoms and signs in vaccinees (thick line) and placebo recipients (thin line).

Upper lines depict the 1st injections; lower (with inverted scale), the 2nd .

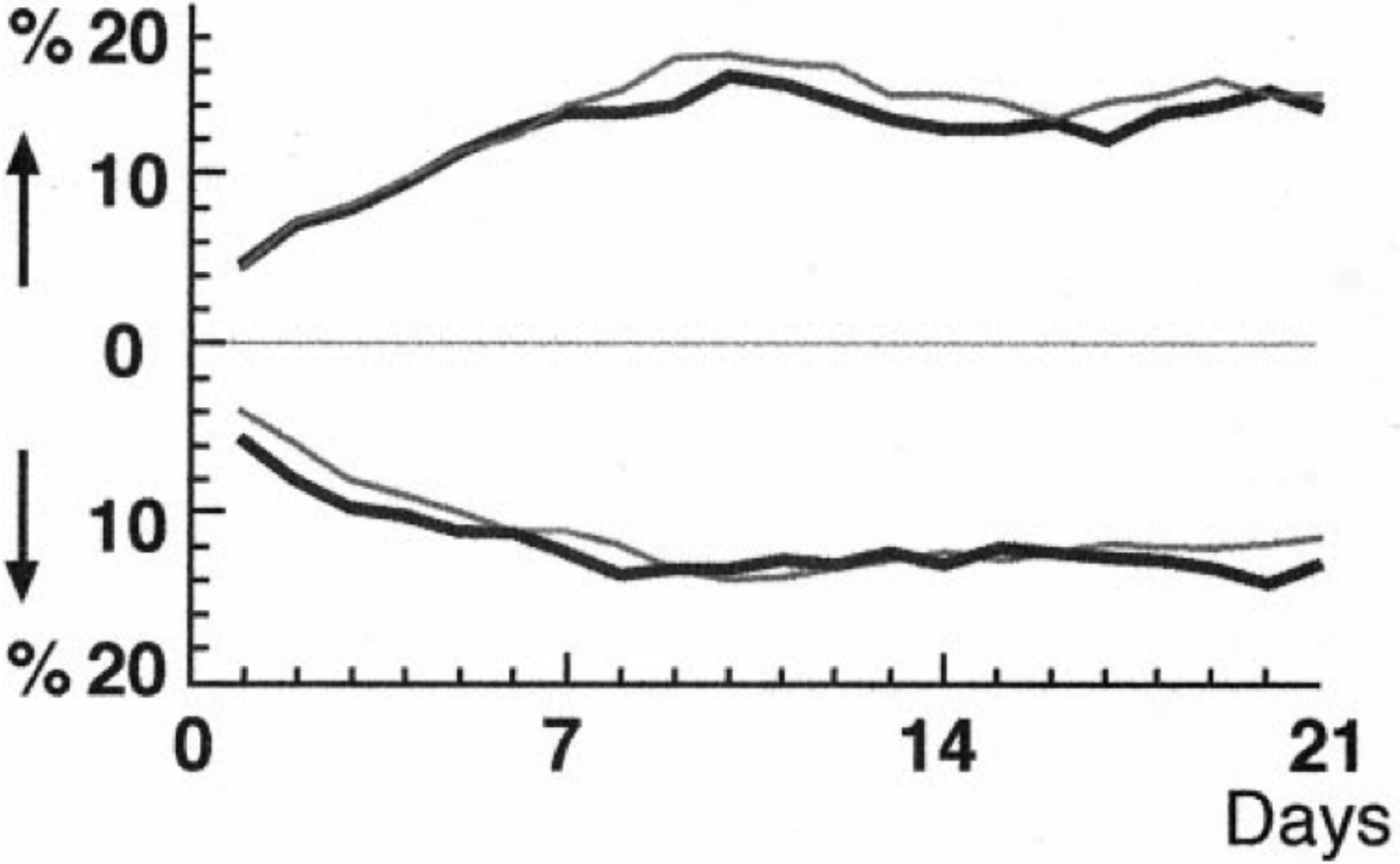

SYSTEMIC
% 20
10
0
10
% 20
1st DOSE
2nd DOSE
0
7
14
21
Days

FEVER




%20
10
0
10
%20
>103.1°F (39.5°C)
0
7
14
21
Days

RESPIRATORY SYMPTOMS



Most interesting was the steady increase in respiratory symptoms and signs for 7 to 9 days post injection in vaccinees, and, surprisingly, in placebo recipients too, without a subsequent decline from the 15% to 20% level reached.

Because vaccinations were given in a relatively symptom-free state, both populations only returned to the usual frequency of trivial symptoms and signs within a week or so post injection. This "healthy vaccinee effect" has never been so indisputably documented before.

Were this phenomenon fully understood—and explained to parents before vaccination—many misunderstandings (and lawsuits) would be avoided.

Results.

Vaccination-attributable events occurred in 6% overall.

At 14 to 18 months of age, reactions developed between days 6 and 14, peaking at day 10. The clearest vaccine-attributable effect was fever exceeding 101.3 °F (38.5°C; odds ratio: 3.28; 95% confidence interval: 2.23–4.82; *P* < .001), but the same trend was found for rash, arthralgia, conjunctivitis, staying in bed, drowsiness, and irritability.

At 6 years of age, systemic reactions occurred 5 to 15 times less frequently, only arthralgia being associated with vaccination. Zygocity, gender, history of allergy, or infections did not modify reactions.

- This study is a response to the need for an adequately controlled study assessing adverse events in relation to MMR that would otherwise not have come to medical attention.
- The short-term reactions in causal association with MMR vaccination proved dramatically less common than was suggested by 3 previous uncontrolled studies.
- Most symptoms and signs commenced 5 to 7 days post vaccination and peaked on day 10 (Figs 1 and 2), suggesting that they were primarily caused by the measles component—the usual incubation period of measles is 8 to 12 days versus 16 to 18 days for rubella and mumps.

- Local reactions (in ~ 4%; Fig 1) were attributable to mechanical trauma, because there was no difference between vaccinees and placebo recipients.
- Regarding systemic reactions, fever was the sign most uniformly caused by MMR vaccination although conditional logistic regression analysis showed the same trend for rash, arthralgia, conjunctivitis, staying in bed, drowsiness, and irritability.
- In contrast, respiratory symptoms and signs (and diarrhea, nausea, and vomiting) were clearly not attributable to MMR vaccination but to other concurrent factors, probably commonplace infections. The presence of these symptoms also understandably increased the probability of fever, arthralgia, conjunctivitis, staying in bed, and irritability.

Instead, respiratory symptoms developed within days postinjection to a level of 15% to 20% without subsequent decline and with no difference between vaccinees and placebo recipients.

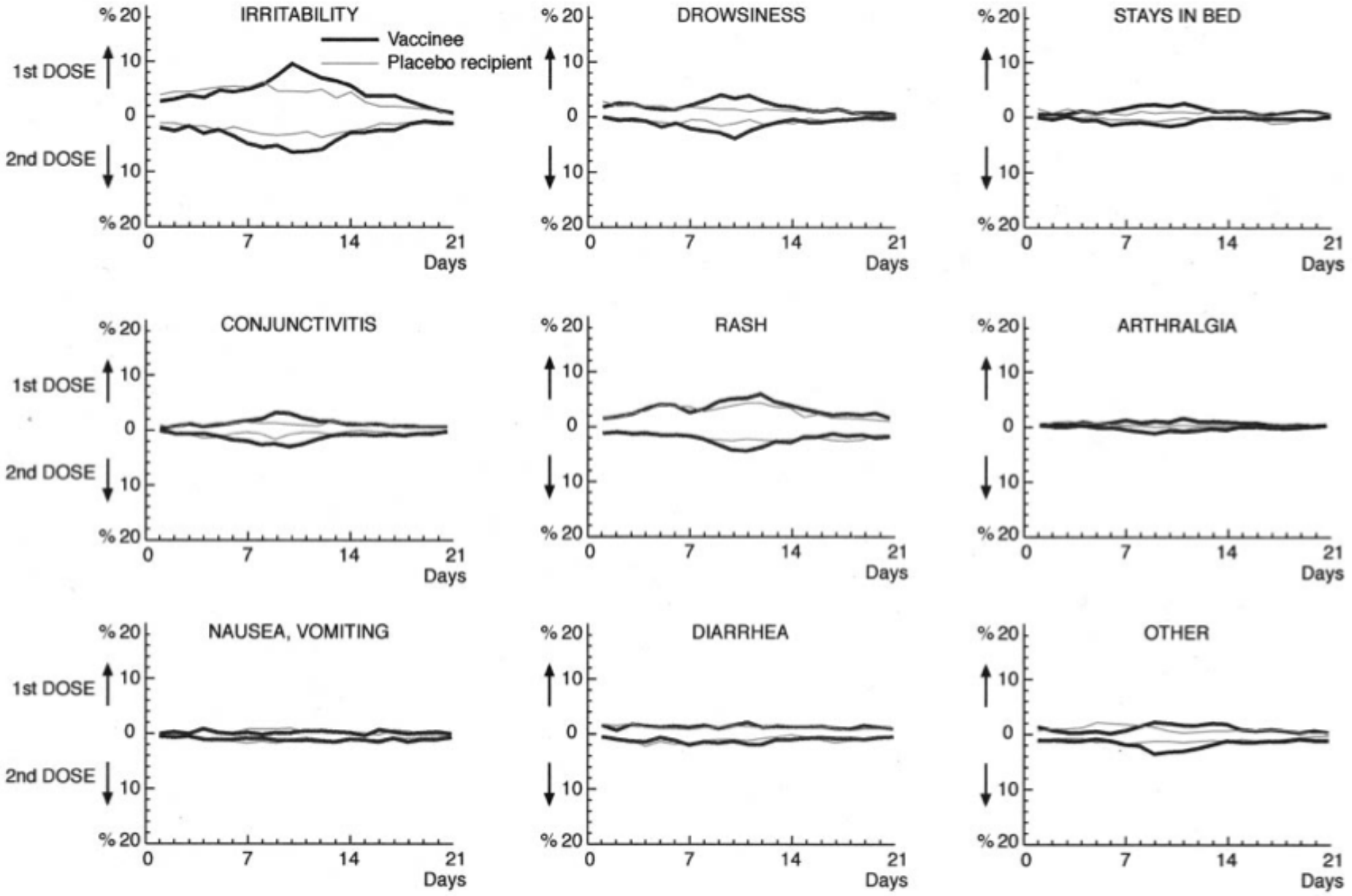


Fig 2. Day-to-day occurrence of other symptoms and signs in vaccinees (thick red line) and placebo recipients (thin green line). The upper lines depict the first injections; the lower (with inverted scale), the second injections.

Nov 1982 – Oct 1983

Table 1. Finnish vaccination programme at time of this study.

Obstetric hospital	<1 mo	BCG I
Child health center	3 mo	PDT I (Pertussis, Diphteria and Tetanus)
	4 mo	PDT II
	5 mo	PDT III + Polio I
	6 mo	Polio II
	14-18 mo	MMR I
	20-24 mo	PDT IV + Polio III
	6 yrs	MMR II
	6-7 yrs	Polio IV
School	11-13 yrs	Polio V + Tetanus V
	13 yrs girls	Rubella
	16-18 yrs	Polio VI
Military		Polio VII + Tetanus VI+ Meningococcus A &C+ Mumps
Whole population	every 5 yrs	Polio
	every 10 yrs	Tetanus
	mothers after giving birth	Rubella
	travellers	According to WHO recommendations
	if needed at epidemics	ex. meningococchus A