Shortage of vaccines during a yellow fever outbreak in Guinea

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A yellow fever epidemic erupted in Guinea in September, 2000. From Sept 4, 2000, to Jan 7, 2001, 688 instances of the disease and 225 deaths were reported. The diagnosis was laboratory confirmed by IgM detection in more than 40 patients. A mass vaccination campaign was limited by insufficient international stocks. After the epidemic in Guinea, the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control decided that 2 million doses of 17D yellow fever vaccine, being stored as part of a UNICEF stockpile, should be used only in response to outbreaks.

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Yellow fever is a viral haemorrhagic fever that is caused by a flavivirus transmitted by mosquitoes. Case-fatality ratios (CFR) exceed 50% in severe instances.[1,2] The disease can be prevented by vaccination with the 17D yellow fever vaccine, which protects for at least 10 years. WHO estimates that 200 000 people in 34 countries of Africa and America, in which the disease is endemic or occurs epidemically, are infected every year, resulting in 30 000 deaths.[1,2] The disease is endemic in rural areas near tropical forests, but large epidemics usually arise when a specific vector (*Aedes aegypti*) transmits the virus in urban settings. Large outbreaks were reported in Ethiopia in 1960 (100 000 cases), in Senegal in 1965 (20 000), and in Nigeria in 1969 (100 000).[1,2] Between 1986 and 1994, more than 20 000 cases were reported in successive epidemics in Nigeria.

In September, 2000, a yellow fever epidemic began in Guinea, where no routine vaccination or reactive mass vaccination campaigns have been done since the end of the 1950s. From Sept 4, 2000, to Jan 7, 2001, 688 cases and 225 deaths were reported (CFR 33%). More than 40 people from 12 different districts had the diagnosis confirmed by ELISA capture and neutralisation tests (IgM detection). During the first 7 weeks of the epidemic, the CFR was more than 60%. However, this rate had fallen by week 42, probably because of better diagnosis of non-haemorrhagic disease, fewer false cases, and improved supportive care. The epidemic peaked in week 47 (between Nov 20 and Nov 26), during which 139 new cases and 46 deaths were reported (figure 1).

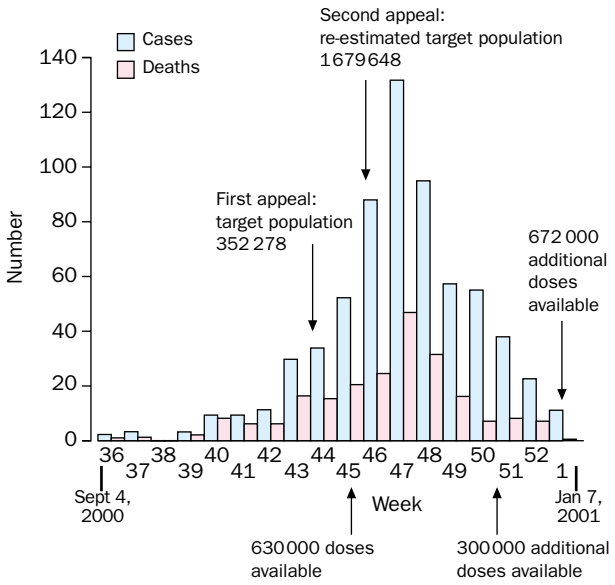

Figure 1: **Yellow fever cases deaths, and details of vaccinations**

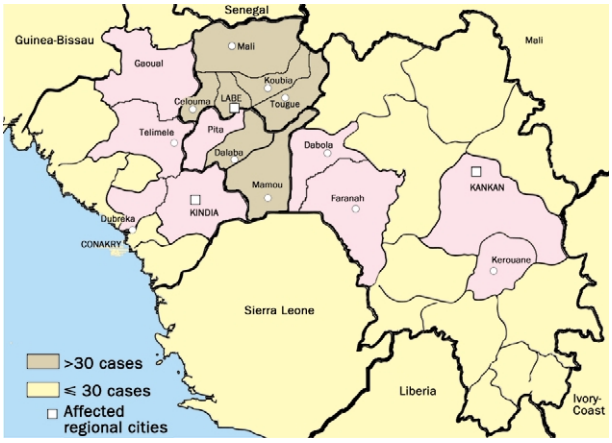

Figure 2: **Areas affected**

For the first 4 weeks, only the Mamou district in the Mamou region was affected. The outbreak then spread to another 16 of the 33 districts of the country (figure 2). The most affected regions were Mamou and Labé, where the alert was sounded on Oct 12 and Nov 6, respectively. In these regions, 80% of individuals with yellow fever lived in rural areas, and district attack rates ranged from 0·1 to 8·0 cases per 10 000 inhabitants. Entomological investigations done in eight of the most affected villages identified only one sylvatic vector breeding site. No *A aegypti* mosquitoes were found in these villages. The low density of *A aegypti* (<5 breeding sites per 100 households) identified in the investigated towns (Labé, Coya, Conakry) prevented the outbreak from developing in the urban setting, where only 78 (12% of the total) individuals in four of the eight main regional cities became ill.

The Guinean Ministry of Health, with the support of international non-governmental organisations, implemented a mass vaccination campaign in response to the epidemic. The initial target population included all individuals aged 9 months or older who were living in Mamou district and in four surrounding unaffected subdistricts (352 278 inhabitants). A first appeal for vaccines was made on Nov 1, 2000. 10 days later, 630 000 doses of vaccine were brought into the country, and vaccination began in Mamou district on Nov 12, 1 week before the peak of the outbreak in that region.

After the alert was given in Labé region, the target population was re-estimated at 1 679 648 people, and a second appeal for vaccines was made on Nov 13. However, no more vaccines arrived in the country until Dec 17 (5 weeks after the second appeal), when 300 000 doses were delivered to Conakry (figure 1). A further 672 000 doses arrived on Jan 5, 2001, of which 150 000 were sent to Labé region. Vaccines were brought from Europe, from the Pasteur Dakar institute, which held stocks of the vaccine, from national stocks in different countries (ie, Niger, Nigeria, and Ghana), and from expanded programmes of immunisation (EPI) in the region. Médecins Sans Frontières, WHO, and UNICEF were the main organisations involved in securing the vaccine stocks.

Because of the shortage of vaccines, mass vaccination campaigns in Labé did not start until 4 weeks after the peak of the epidemic in that region. Furthermore, vaccination strategies had to be revised and target populations restricted to affected urban areas and to worst affected rural areas. At the end of the intervention, just 9 weeks later, 856 031 individuals had been vaccinated in Mamou and Labé, where the overall vaccine coverage was estimated at 56%. The Ministry of Health and MSF continued mass-vaccination campaigns in other regions and used up the available stocks.

Yellow fever epidemics are re-emerging in Africa and America, and the occurrence of repeated rural outbreaks increases the risk for major urban epidemics.[3,4] However, as

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shown by the Guinean episode, the international stocks of yellow fever vaccines are not sufficient to provide an adequate and rapid response to large outbreaks. In 2000, an alert was sounded in Kano city (1·5 million inhabitants), Nigeria. No epidemic occurred, but had there been one the stocks of vaccines would not have been adequate (unpublished data, Epicentre, July, 2000). During the yellow fever consensus meeting, WHO recommended that an emergency stockpile of 1 million doses be retained in Africa and America for outbreak response.[2] Furthermore, after the epidemic in Guinea, the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control decided that 2 million doses, being stored as part of a UNICEF stockpile, should be used only in response to outbreaks. If effective, this stock should limit shortages of vaccines during future epidemics. However, prevention of yellow fever epidemics can only be addressed by organising pre-emptive mass vaccination campaigns or by a large and effective introduction of yellow fever vaccination in the EPI of the countries at risk, as recommended by WHO.

1 WHO. Yellow fever: WHO/EPI/GEN/98.11. Geneva: WHO, 1998.
2 WHO. Yellow fever technical consensus meeting: HO/EPI/GEN/98.08. Geneva: WHO, 1998.
3 WHO. Yellow fever, 1996–1997, part I. *Wkly Epidemiol Rec* 1998; **73:** 354–59.
4 WHO. Yellow fever, 1996 –1997, part II. *Wkly Epidemiol Rec* 1998; **73:** 370–72.

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Blood-pressure reduction and cardiovascular risk in HOPE study

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In the Heart Outcomes Prevention Evaluation (HOPE) study, use of the angiotensin-converting-enzyme inhibitor ramipril was associated with a 22% relative risk reduction in cardiovascular death, myocardial infarction, or stroke, despite only a modest reduction in blood pressure (−3·3 mm Hg systolic). To test the hypothesis that the benefits seen were not due to reduced blood pressure alone, we calculated blood-pressure-related risk estimates from the placebo group of the HOPE trial, and from earlier studies. We found that the benefits seen in HOPE were around three times greater than predicted from these calculations. In this well treated and largely normotensive population with coronary disease, but good left-ventricular function, the benefits from ramipril were additive to other proven therapies in normotensive patients and in those with higher baseline blood pressure.

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Angiotensin-converting-enzyme (ACE) inhibitors lower blood pressure, but have other potentially protective actions on left-ventricular hypertrophy, endothelial function, and smooth-muscle growth. In the Heart Outcomes Prevention Evaluation (HOPE) study,[1] ramipril (10 mg per day) lowered blood pressure only modestly (by 3·3/1·4 mm Hg) in high-risk, mostly normotensive patients, but still reduced the primary endpoint (cardiovascular death, myocardial infarction, or stroke) over 4·5 years by 22%, independent of other established treatments of known hypertension. There is controversy about the view that these benefits are not explained by the blood-pressure reduction seen. We now present further analyses of the relation between the observed benefit and baseline blood pressure, and degree of blood pressure reduction, together with estimates of what might be expected from previous data on blood pressure and risk, as well as from estimates derived from the placebo group of HOPE.

Data source	Difference in systolic blood pressure (mm Hg)	Relative risk reduction	
		Myocardial infarction	Stroke
WHO/ISH* guidelines	10–15	15	40
HOPE			
Ramipril group			
Estimated†	3·3	5	13
Observed	3·3	20	32
Placebo group			
Estimated	3·3	5·5	7

*International Society of Hypertension. †Derived from WHO/ISH.

Table 1: **Estimates of risk reduction for stroke and myocardial infarction for a given difference in systolic blood pressure**

In HOPE, blood pressure was measured in duplicate by trained nurses after 5 min rest at baseline, 1 month, 2 years, and at study end. We calculated the "usual" blood pressure by averaging all available blood pressures in the placebo patients free of myocardial infarction. By use of a Cox's regression analysis, we related differences in systolic blood pressure to differences in risk of the primary outcome in our placebo group. This estimate of blood-pressure-related risk was also compared with similar calculations derived from independent observational analyses from other studies, and that derived from a meta-analysis of all trials (referred to jointly as WHO/ISH in table 1). These two independent blood-pressure-related risk estimates were then compared with the observed risk reduction from ramipril. We also compared the benefits of ramipril above and below the median baseline blood pressure (138 mm Hg systolic and 80 mm Hg diastolic).

The observed benefit from ramipril was much greater than expected from the blood-pressure reduction in HOPE (table 1), estimated either from earlier studies, or from the experience in the HOPE placebo-group patients, who were at higher risk than those in previous hypertension trials.

The relative risk of the primary outcome for ramipril versus placebo (0·78 [95% CI 0·70–0·86]) did not change after adjustment for time-dependent change in systolic blood pressure and diastolic blood pressure. For each separate component of the primary outcome (myocardial infarction, stroke, and cardiovascular death), the unadjusted and adjusted relative risks were respectively 0·80 (0·70–0·90) and 0·77 (0·65–0·91); 0·68 (0·56–0·84) and 0·72 (0·58–0·89); and 0·74 (0·64–0·87) and 0·77 (0·65–0·91). Significant benefit was also seen in the normotensive population comprising those with baseline blood pressure below the median of 138/80 mm Hg (table 2).

The benefits from ACE inhibition were independent of, and additive to, those from other proven hypertension therapies. The relative risk of the primary outcome with or without β-blockade, diuretics, or calcium-channel blockers were, respectively, 0·77 (0·65–0·90) versus 0·78 (0·68–0·89); 0·75 (0·59–0·94) versus 0·78 (0·70–0·88); and 0·84 (0·73–0·97) versus 0·71 (0·61–0·83). In each of these six comparisons of ramipril versus placebo, there was significant benefit from ramipril for the primary outcome ($p<0·01$), with no significant evidence of heterogeneity.

In a high-risk population (80% had previous coronary disease, but normal baseline blood pressure and left-ventricular function), ramipril confers substantial benefits which are additional to those from other antihypertensive medication and greater than expected from the modest blood-pressure reduction. These benefits are similar in importance to those of aspirin and statins in protection against further serious events.[3]

There has been speculation that the relatively few

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