agents cause limited damage. However, more malignant forms of "auto-mutilating" hoaxes are likely to emerge that could be as devastating to computers as some autoimmune diseases are to humans.

The electronic monoculture that improves communication also increases the risk for contagion. Predominant use of a single operating system has improved communication and sharing of electronic data but has also facilitated ready amplification of virulent programs. As with biological infection, transmission of computer infection depends on susceptibility of the population. Virus producers saw an opportunity in the popular preference worldwide for PCs with Microsoft Windows operating systems. The enormous popularity of these systems, along with their long-recognized inadequate protection against misuse, made computer users susceptible. Virtual viruses able to infect multiple operating systems are rare (as are biological viruses with broad host specificity), and even when infected, computers that run on different operating systems (e.g., Mac, Unix) or other-than-Outlook e-mail programs usually are dead-end hosts for PC viruses.

Pathogens do not reinvent the wheel. Virulence genes are constantly "stolen" and reused. Thus, new combinations of virulence genes can result in new pathogenic strategies, and such combinations frequently accumulate in pathogenicity islands. Reuse and combination of effective (and infective) strategies are also common in computer malware. A recent example demonstrates the value of just the right amount of virulence. A highly dangerous worm called Nimda (Admin in reverse) was released exactly 1 week after the September 11, 2001, terrorist attack in the United States. Nimda combined the most powerful strategies of Code Red and SirCam and spread more rapidly than any previous worm. Clicking on the subject line of an infected e-mail (to delete it, for instance) itself activated the worm. However, because of the immensity of the threat, the Internet community responded extremely rapidly. Within hours after its release, alerts to system administrators on how to block the worm had effectively slowed its spread. Early surveillance and barrier development averted disaster. As in contained epidemics of hemorrhagic fevers, the immense threat of high contagion and lethality prompts effective measures to rapidly recognize outbreaks and prevent pandemics.

The types of measures to be used against computer contagion can be learned from biology. Immune effectors of plants and animals protect against a broad range of pathogens; however, in nature this system evolved over millions of years. Engineering protective computer systems with similar efficacy within a few years is a great challenge. Current protection programs mainly resemble innate immunity, but programs that learn from exposure (thus resembling adaptive immunity) are under development. Vaccination with relatively harmless microbes primes the immune system. Biological hosts also naturally carry protective microflora that compete with pathogens. Could we produce "virtual vaccines" that are beneficial to the computers carrying them (e.g., by blocking preferred sites of entrance for viruses or repairing viral damage automatically) and let these "good" microbes circulate on the Internet just as malignant viruses do? Crude versions of such vaccines have already been developed. Using "good" microbes would have its costs: occupation of Internet capacity and consequent slowdown of data transmission and presence of malicious worms disguised as beneficial ones to elude detection.

Knowledge of infectious diseases may help control computer contagion. Conversely, study of computer malware may help curb infectious disease emergence. Internet contagion illustrates how pathogens emerge and spread in our increasingly small world. The speed of virtual pathogen evolution makes it possible to follow the process of mutation and selection in real-time. With countless interlinked computers, the risk for virtual contagion is so great that urgent steps are needed to avoid catastrophe. How many pandemics will it take before we accept the risks and costs of computer immunity? Similarly, to protect against emerging pathogens, we must use all tools available, including virtual pandemics. A task force to collect data on the epidemiology of virtual infections as a model for infectious diseases might be an important first step.

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Emergence and Rapid Spread of Tetracycline-Resistant *Vibrio cholerae* Strains, Madagascar

To the Editor: The Indian Ocean was free of cholera for decades, until January 1998, when an outbreak was detected in Comoros Islands (1). On March 23, 1999, the Malagasy Epidemiological Surveillance System reported the first case of cholera in Mahajanga, a harbor on the northwest coast (2). In May 1999, the Malagasy sanitary authorities set up sanitary barricades at the borders of the two provinces—Mahajanga and Antananarivo—affected by the epidemic. Oral doxycycline was systematically given to all the travelers crossing the barricades. In addition, doctors in hospitals and dispensaries in these two provinces gave doxycycline to patients

with acute diarrhea. Despite these measures, cholera had reached all six provinces of the island 10 months later. In June 1999, a specific cholera surveillance system was established in every Malagasy province with close collaboration between the Malagasy Ministry of Health and the Institut Pasteur de Madagascar.

The first strain isolated in Mahajanga was *Vibrio cholerae* serogroup O1, serotype Ogawa, biotype El Tor. Its antibiotype showed resistance to trimethoprim-sulfamethoxazole, sulfonamides, trimethoprim, chloramphenicol, streptomycin, and vibriostatic agent O129 (a molecule naturally active against *V. cholerae* and used for identification). Susceptibility was conserved for tetracycline, ampicillin, cephalotin, and pefloxacin (2). This strain showed a rRNA gene restriction pattern similar to those of African and Comorian strains isolated since 1994 and 1998, respectively (2,3).

From July 1999 to March 2001, we monitored the tetracycline resistance of *V. cholerae* isolated from the stool samples sent to the Institut Pasteur de Madagascar in Antananarivo, using the standard disk-diffusion method (4). Stool samples were collected in sterile containers, on Whatman paper, or on rectal swabs. Isolation of *V. cholerae* was carried out immediately after reception. Every *V. cholerae* strain identified belonged to serogroup O1, biotype El Tor. All the tetracycline-resistant *V. cholerae* isolated and 60 randomly selected tetracycline-susceptible strains were tested for sensitivity to the following drugs: ampicillin, cephalotin, doxycycline, sulfonamide, trimethoprim, trimethoprim-sulfamethoxazole, chloramphenicol, streptomycin, spectinomycin, neomycin, kanamycin, nalidixic acid, pefloxacin, erythromycin, rifampicin, and nitrofurantoin, as well as to vibriostatic agent 0129.

During the study period, we isolated 351 (46.1%) *V. cholerae* strains from 761 stool samples analyzed. The provinces of Antananarivo, Mahajanga, and Toliary accounted for 85.9% of the stool samples sent to our laboratory. From these provinces, we isolated 288 strains; by contrast, from the three other provinces (Antsiranana, Fianarantsoa, and Toamasina, located on the east coast), 63 strains were isolated. Rates of isolation, tested by a chi-square test, did not differ significantly between the six provinces ($p=0.32$).

Fifty five (15.7%) of the 351 strains isolated were found to be tetracycline resistant (cross-resistance with doxycycline) but had the same resistance pattern as the index strain isolated in Mahajanga for the other antibiotics tested. During the first rainy season following the epidemic (November 1999 to March 2000), a unique tetracycline-resistant strain

was isolated (in February 2000), in the capital Antananarivo; it was also resistant to ampicillin, nalidixic acid, and nitrofurantoin. During the dry season (from April to October 2000), five (13.2%) of 38 *V. cholerae* new tetracycline-resistant strains were found. However, during the last rainy season (November 2000 to March 2001), 49 (69 %) of 71 strains isolated were tetracycline resistant. They were mainly from the city and suburbs of Antananarivo (95.3%, 41/43 strains). The eight other resistant strains came from the provinces of Antananarivo, Toliary, and Fianarantsoa.

As observed in Tanzania (5), the extensive prophylactic use of tetracycline may have triggered the rapid emergence and spread of tetracycline-resistant strains in Madagascar. The high rate of resistance in Antananarivo, where the major Malagasy hospitals are located, could be due to easier access to drugs in the capital than in the other provinces.

Of the 60 randomly selected tetracycline-susceptible strains, 56 had the original antibiotype; four became susceptible to vibriostatic agent O129 and to all the antibiotics tested, except trimethoprim. Four (3.5%) of the 115 strains tested (55 tetracycline-resistant and 60 tetracycline-susceptible strains) on a large panel of antibiotics were susceptible to trimethoprim-sulfamethoxazole. As usually observed in other African cholera-endemic countries (6), only a small proportion of the strains were susceptible to trimethoprim-sulfamethoxazole, one of the most frequently dispensed drugs.

Faced with this first emergence of cholera in Madagascar and its rapid spread, medical authorities reacted immediately by using doxycycline as chemoprophylaxis (contrary to World Health Organization recommendations [7]), probably because of its easy availability**.**

Our study demonstrates that 2 years after the epidemic began, neither trimethoprim-sulfamethoxazole nor tetracycline, the two first-line drugs used in Madagascar, can be recommended any longer for treating severe cases of cholera. This may represent a critical public health problem in the country, especially as most of the population cannot afford more effective but expensive antibiotics.

Therefore, Malagasy medical authorities should a) abandon any systematic chemoprophylaxis, b) advise only oral rehydration therapy for mild-to-moderate cases, and c) reserve antibiotic therapy for severe illness (7). These measures against the cholera epidemic should be accompanied by general reinforcement of microbiologic surveillance to monitor antibiotic resistance so that the island can respond effectively to any future bacterial epidemics.

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References

1. World Health Organization. Cholera in the Comoros Islands. Wkly Epidemiol Rep 1998;5:32.
2. Duval P, Champetier de Ribes G, Ranjalahy J, Quilici ML, Fournier JM. Cholera in Madagascar. Lancet 1999;353:2068.
3. Germani Y, Quilici ML, Glaziou P, Mattera D, Morvan J, Fournier JM. Emergence of cholera in the Central African Republic. Eur J Clin Microbiol Infect Dis 1998;17:888-990.
4. National Committee for Clinical Laboratory Standards (NCCLS). Performance standards for antimicrobial disk susceptibility test: approved standard M2-A6. Wayne (PA): The Committee;1997.
5. Mhalu FS, Mmari PW, Ijumba J. Rapid emergence of El Tor *Vibrio cholerae* resistant to antimicrobial agents during first six months of fourth cholera epidemic in Tanzania. Lancet 1979;1:345-7.
6. Materu SF, Lema OE, Mukunza HM, Adhiambo CG, Carter JY. Antibiotic resistance pattern of *Vibrio cholerae* and *Shigella* causing diarrhoea outbreaks in the eastern Africa region: 1994-1996. East Afr Med J 1997;74:193-7.
7. World Health Organization. Guidelines for cholera control. Geneva: World Health Organization; 1993.

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