Containing Bioterrorist Smallpox

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The need for a planned response to a deliberate introduction of smallpox has recently become urgent. We constructed a stochastic simulator of the spread of smallpox in structured communities to compare the effectiveness of mass vaccination versus targeted vaccination of close contacts of cases. Mass vaccination before smallpox introduction or immediately after the first cases was more effective than targeted vaccination in preventing and containing epidemics if there was no prior herd immunity (that is, no prior immunologic protection within the population). The effectiveness of postrelease targeted and mass vaccinations increased if we assumed that there was residual immunity in adults vaccinated before 1972, but the effectiveness of targeted vaccination increased more than that of mass vaccination. Under all scenarios, targeted vaccination prevented more cases per dose of vaccine than did mass vaccination. Although further research with larger-scale structured models is needed, our results suggest that increasing herd immunity, perhaps with a combination of preemptive voluntary vaccination and vaccination of first responders, could enhance the effectiveness of postattack intervention. It could also help targeted vaccination be more competitive with mass vaccination at both preventing and containing a deliberate introduction of smallpox.

Recent public debate has focused on choosing a response to an intentional release of smallpox in the United States (*1*). Routine vaccination against smallpox in the United States was stopped in 1972, leaving a substantial portion of the population susceptible. No one is certain how much residual protection is conferred by smallpox vaccinations received before 1972 (*2*). Options for responding to a smallpox release include preemptive voluntary vaccination to increase herd immunity (immunologic protection within the population) (*3*); postrelease surveillance and containment, or ring vaccination, in which confirmed or suspected cases are isolated and their contacts are traced and vaccinated (*4*); and vaccination of large numbers of first responders, with plans for postrelease mass vaccination (*5*, *6*).

To compare the effectiveness of targeted vaccination versus mass vaccination, we constructed a discrete-time, stochastic simulation model of smallpox spread within a structured community. We also examined the effect of assuming residual immunity in adults vaccinated before 1972. We explored what we consider to be the most likely method of attack, namely, a few infected individuals moving through the community.

Our model simulated the stochastic spread of smallpox in communities of people interacting in known contact groups (*7*, *8*). For each simulation, a community of 2000 people was stochastically generated on the basis of the age distribution and approximate household sizes from U.S. Census 2000 (*9*). Each community had four neighborhoods, one high school, one middle school, and two elementary schools. Preschool children attended either small play groups or larger day care centers. Households had 1 to 7 people per family (mean was 2.3 people), with 33% of households being made up of single adults. Person-to-person transmission probabilities were highest in households; lower in the day care centers, play groups, and schools; and even lower in the neighborhoods and the community at large (table S1). Each day, for each susceptible person, the probability of becoming infected was calculated on the basis of the person's vaccination status, who was infectious in the person's contact groups and their vaccination status, and the group-specific transmission probabilities. We assumed that everyone over 30 years of age (~57% of each community) was vaccinated against smallpox before 1972.

Smallpox natural history has three main phases (*10*, *11*) (Fig. 1). In our model, people in the prodromal period withdrew with some probability to the home, exposing only the other members of their household; all people stayed home within 3 days of developing pox. Calibration of the model was based on historical data available on smallpox, including household secondary attack rates (*10*), relative age-specific attack rates (the rates are higher in children) (*12*), and numbers of secondary cases produced by an introductory case (*10*, *13*).

For fresh vaccination, the protective vaccine efficacy for susceptibility was assumed to be $VE_S = 0.95$ (*14*) and multiplicative on the transmission probability (*14*). Vaccine efficacy for infectiousness (*14*) was assumed to be $VE_I = 0.80$. For people vaccinated before 1972, we assumed a worst-case scenario in which these individuals had no residual immune protection against infection, disease, or death. Under a second scenario, we assumed that people vaccinated before 1972 had infection protection that was about half that provided by fresh vaccination, with $VE_S = 0.50$. If infection occurred, $VE_I = 0.80$, and the case fatality ratio was 0.03. People vaccinated before 1972 could be freshly vaccinated in the interventions.

We explored two scenarios of mass vaccination. In the first, mass vaccination occurs before smallpox is introduced. In the second, mass vaccination occurs after the epidemic begins, with vaccination taking place over 10 days once it is initiated. For mass vaccination before smallpox introduction, we examined coverage levels of 30, 50, and 80%; and for mass vaccination during an epidemic, we examined a coverage level of 80%. Under the targeted vaccination strategy, individuals in close contact groups of ascertained index smallpox cases are vaccinated. We simulated

Incubation	Prodromal	Pox
• 10-14 days	• 3-5 days	• 14-17 days
• 12 day mean	• 4 day mean	• 15.5 day mean
• 100% of infected people ill by end of day 14	• highly infectious	• infectiousness: 10% of prodromal phase
• sensitive to vaccine during first 3 days after infection	• probability of withdrawal by day 3:	• withdrawal over first 3 days (100% by 3rd day)
	preschool: 0.8	• recovered/removed after completing this phase
	school: 0.75	
	adult: 0.50	

Fig. 1. Natural history of smallpox infection in our model. The duration of each of the three main periods is uniformly distributed between its minimum and maximum periods. During the prodromal period, the probability of people's staying home by the third day of symptoms is similar to the probability given by the influenza model in (*21*). All people stay home within 3 days of developing pox.

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two levels of ascertainment: 80 and 100%. When an index case is ascertained, the person's entire household is vaccinated. If the ascertained index case is also in a day care center or play group, all individuals in the day care center or play group are vaccinated. If the index case is in a school, then either 80 or 100% of the children in the school are vaccinated. For both ascertainment levels, 1.5% of the contacts in the same neighborhood (that is, 7 or 8 of ~500 people) as that of each recognized index case are also vaccinated. To model a possible delay in response, we assumed that interventions begin after either the 1st ascertained indigenous case, the 15th case (about day 20 after the 1st case), or the 25th case (about day 30 after the 1st case).

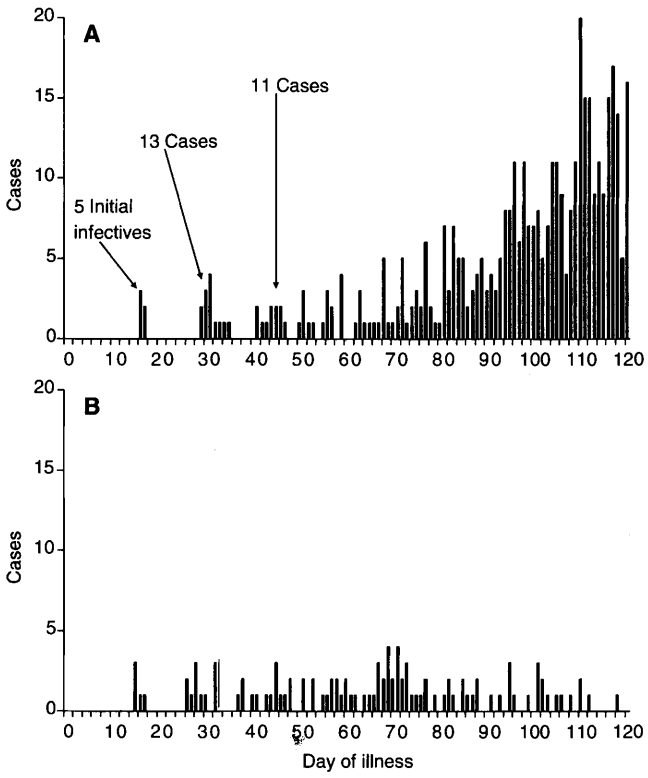

Fig. 2. The first 120 days of typical stochastically simulated smallpox epidemics with five initial infective persons in communities with no prior residual immunity in people who are 30 years of age and older. (**A**) Baseline with no intervention. (**B**) Intervention with targeted vaccination, with 100% ascertainment begun after the first indigenous secondary case. The simulated epidemics without intervention last on average ~300 days.

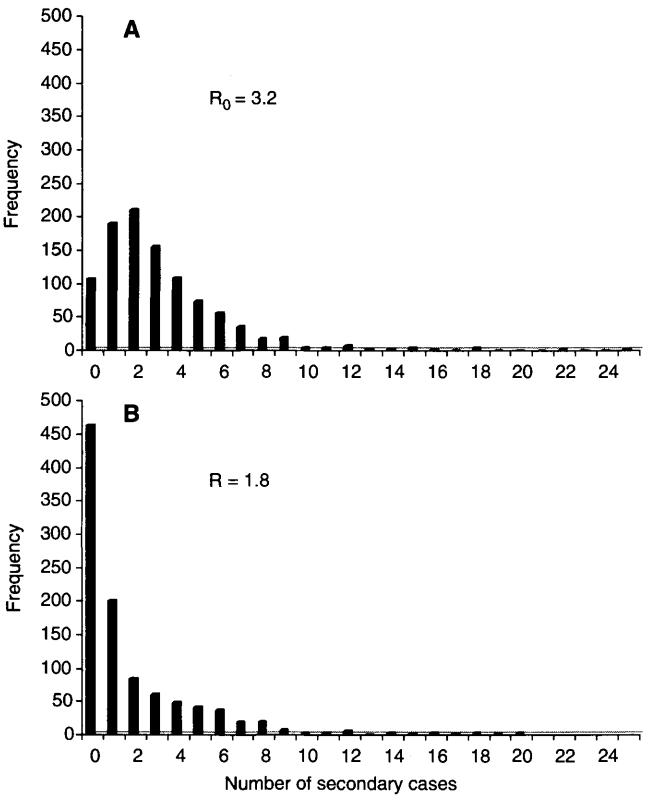

Fig. 3. R_0 and R. (**A**) The number of secondary cases produced by a random person if the community has no residual immunity (R_0). (**B**) The number of secondary cases produced by a random person if the adults over 30 years of age have residual immunity from vaccination before 1972 (R). To examine R and R_0, we assumed a scenario in which one randomly chosen, unvaccinated infective person was seeded into a community where everyone else's ability to transmit was 0, and then we counted the number of secondary cases. The initial infective person does not stay home after developing symptoms. This was repeated 1000 times for each scenario.

In 200 simulations of each intervention, smallpox was introduced by one or five unvaccinated adults per each community of 2000 persons. To simulate deliberate introduction, we assumed that the initial infective persons did not live with children, began circulating at the beginning of their prodromal period, and did not stay home during the prodromal period or once they developed pox. The three measures of intervention effectiveness (defined in Table 1) are the epidemic prevention potential (EPP) (*8*), the containment effectiveness (C_{Eff}) and the average overall effectiveness (VE_{III}) (*14*). We define the threshold of a major epidemic as an attack rate of >2.5%.

Our simulator reproduced the typical ~14- to 16-day generation time observed in smallpox epidemics (Fig. 2). We empirically explored the basic reproductive number R_0: the average number of infective persons that one infective individual will produce in a particular completely susceptible population (*15*) (Fig. 3A). With our model, assuming no residual immunity, we found that the empirical R_0 = 3.2, with a range of secondary cases from 0 to 25. We also examined the reproductive number R: the average number of infective persons that one infective individual will produce in a population that has some preexisting immunity (Fig. 3B). Assuming residual immunity in adults, we found that the empirical R = 1.8 (range of secondary cases from 0 to 20). We found that an unvaccinated adult without children, as was used to introduce infection in these simulations, produced on average 1.7 secondary cases (range from 0 to 8; 19% produced 0 cases) and 1.1 secondary cases (range from 0 to 6; 34% produced 0 cases), assuming no residual immunity in adults and residual immunity in adults, respectively (table S2).

Residual immunity in adults substantially lowers both the probability of a major epidemic and the baseline attack rate if an epidemic occurs. In contrast, the probability that a major epidemic occurs is sensitive to the number of initial infective persons, but the attack rate if an epidemic occurs is not (*16*) (fig. S1). With five initial infective persons, 63 and 97% of the epidemics are major with and without residual immunity, respectively. With one initial infective person, 15 and 51% are major with and without residual immunity, respectively. The average attack rates conditional on a major epidemic are 0.36 and 0.63 with and without residual immunity, respectively. With residual immunity in adults, the overall average attack rates are 0.05 and 0.23 with one and five initial infec-

Table 1. Cases, doses, and effectiveness of interventions with five initial unvaccinated adult infective persons in communities of 2000 people. The results are based on 200 simulations for each scenario. VE_{III} (*14*) is 1, minus the average attack rate in the intervention communities divided by the average attack rate in the baseline communities, regardless of whether the attack rate exceeds a certain threshold or not. EPP is 1 minus the relative probability of the overall attack rate exceeding a certain threshold in the intervention communities as compared to the nonintervention communities (*8*). C_{Eff} of an intervention, given that an epidemic has exceeded a certain defined threshold, is 1, minus the average attack rate in communities with intervention with a major epidemic divided by the average attack rate in nonintervention communities with a major epidemic. The threshold of a major epidemic is defined as an attack rate of >2.5%.

Intervention	No residual immunity					With residual immunity				
	Cases per 2000	Doses per 2000	VE_{III} (%)	C_{Eff} (%)	EPP (%)	Cases per 2000	Doses per 2000	VE_{III} (%)	C_{Eff} (%)	EPP (%)
None	1222	–	–	–	–	456	–	–	–	–
Vaccination before any cases										
30%	634	597	48	41	12	177	599	61	47	29
50%	166	996	85	78	43	44	996	90	75	68
80%	20	1597	98	94	94	12	1594	97	92	98
80% mass vaccination after any cases										
1st case	42	1587	97	93	71	16	1567	96	90	93
15th case	170	1506	85	85	4	92	900	80	79	6
25th case	253	1457	79	76	2	131	858	71	69	10
80% targeted vaccination after any cases										
1st case	180	572	85	84	10	26	263	94	90	75
15th case	263	613	79	78	3	87	318	81	81	0
25th case	358	666	70	70	1	125	342	72	73	0
100% targeted vaccination after any cases										
1st case	115	610	90	89	14	19	295	96	92	91
15th case	187	683	85	84	1	67	346	95	92	39
25th case	280	739	77	76	1	97	357	79	78	6

Table 2. Death rate, VE_{III}, and cases prevented per dose by intervention with one initial infective person in communities of 2000 people. The results are based on 200 simulations for each scenario. Cases were multiplied by the vaccine-status–specific case fatality ratio, which is 0.3 and 0.03 in unvaccinated and vaccinated cases, respectively (*10*).

Intervention	No residual immunity			With residual immunity		
	Deaths per 1000	VE_{III} (%)	Cases prevented per dose	Deaths per 1000	VE_{III} (%)	Cases prevented per dose
None	97.2	–	–	12.4	–	–
80% mass vaccination after any cases						
1st case	0.9	99	0.50	0.2	97	0.11
15th case	9.4	86	0.77	2.4	74	0.32
25th case	13.7	80	0.73	3.3	66	0.28
80% targeted vaccination after any cases						
1st case	10.9	88	2.01	0.5	95	1.44
15th case	19.6	78	1.57	1.8	83	0.69
25th case	28.2	68	1.17	4.0	69	0.66

tive persons, respectively; with no residual immunity, they are 0.32 and 0.61, respectively (fig. S2).

Tables 1 and 2 present the intervention results with five and one initial infective persons, respectively, with cases shown in Table 1 and death rates in Table 2. After the introduction of smallpox, 80% mass vaccination, begun after the first secondary case, does very well and is more effective than 80% targeted vaccination. There is, however, a price for choosing 80% postattack vaccination over preemptive mass vaccination, because the proportion of major epidemics is greater and the numbers of cases and subsequent deaths are higher. With no residual immunity, targeted vaccination has a poor EPP. However, the overall and containment effectiveness of 100% targeted vaccination are nearly as high as those of 80% mass vaccination if the response is delayed.

Assuming residual immunity in adults vaccinated before 1972, we found that the effectiveness of both mass vaccination and targeted vaccination was increased. However, residual immunity increases the effectiveness of targeted vaccination more than it increases the effectiveness of mass vaccination. With residual immunity, targeted vaccination becomes competitive with mass vaccination, especially if response is delayed. When implemented immediately, the targeted strategies have a good EPP if there is residual immunity. The number of cases prevented per dose is higher with targeted than with mass vaccination (Table 2). Assuming residual immunity in adults, we found that the number of cases prevented per dose is lower for all strategies than when assuming no residual immunity, because there are fewer baseline cases to prevent.

The overall effectiveness (VE_{III}) of the various strategies is nearly identical whether one or five initial infective persons per community of 2000 are used, representing a range of baseline attack rates from 0.05 to 0.61 (Tables 1 and 2). Other measures, such as the relative cases prevented per dose under mass versus targeted vaccination, without or with residual immunity in adults, are similarly robust. Thus, the relative qualitative behavior of targeted versus mass vaccination is robust over a range of both the number of initial infective persons and baseline attack rates.

The number of vaccine-related deaths was generally lower in the targeted strategies than in the analogous mass vaccination strategies because fewer doses were used (*17*). Because the vaccine-related fatality rate is $\sim 10^{-6}$ (*18*), vaccine-related deaths are greatly outnumbered by smallpox deaths once a large outbreak occurs.

In the sensitivity analysis of targeted vaccination, vaccinating 10% rather than 1.5% of the neighborhood contacts of an index case slightly improved all effectiveness measures. Assuming that no one stays home during the prodromal period, we found that the average baseline attack rates increased from 0.61 to 0.83 with no residual immunity and from 0.23 to 0.39 with residual immunity. We also found that the effectiveness of all interventions was lower (particularly the EPP), with the effectiveness of targeted vaccination decreasing more than that of mass vaccination. People simply staying home when they are

infectious reduces transmission and increases the effectiveness of vaccination.

Although our stochastic simulator requires additional refinements to model a large U.S. community adequately, its findings, which are substantially different from those of other recent modeling efforts (*5*), indicate the importance of detailed modeling of contact patterns in understanding how to contain a possible bioterrorist attack. Similar to the results of others (*5*), our results suggest that timely mass vaccination could be more effective than targeted vaccination in preventing and containing epidemics if there is no preexisting immunity. However, our structured simulator does not produce the two orders of magnitude difference between the two strategies, which was obtained by others using a homogeneous mixing model that assumes that people interact with millions of others equally and simultaneously (*5*). In addition, substantial, although by no means complete, preexisting herd immunity improves both mass and targeted vaccinations. However, targeted vaccination improves relatively more and becomes competitive with mass vaccination. Targeted vaccination prevents more cases per dose. It would be the preferred intervention if the supply of vaccine were limited or if vaccine-related side effects were to be minimized. For all strategies, rapid response can make the difference between preventing and merely containing an epidemic.

Our stochastic heterogeneous simulator reproduces the expected day-by-day incidence of epidemic smallpox. In contrast to deterministic models, stochastic simulations produce a range of outcomes corresponding to the probabilistic nature of epidemics. Stochastic models are particularly useful for studying a few initial infective persons in a community, as well as the timing of early events. The variability in the number of secondary cases produced by one initial infective person in our simulations compares favorably with historical data from Europe (table S3) (*10*). The median and mean size of the first generation from a single index case were 2.0 and 5.1 cases, respectively. Our simulated mean values of $R_0 = 3.2$ and $R = 1.8$ are somewhat lower than recent estimates of R_0 for smallpox between 3.5 and 6 (*19*). However, the data used in that analysis have an ascertainment bias because larger epidemics tend to be ascertained. Currently, R_0 and R values could be lower in the United States than they used to be (because nearly 30% of households consist of one individual) or than they still might be in countries with other social structures. A person with smallpox who interacts closely with many other people, such as in a school or in a hospital, will infect a large number of people. The many observed hospital-based smallpox outbreaks (*10*) provide a strong argument for vaccinating first responders.

Our model's basic community is made up of 2000 people in identifiable contact groups, because individuals are unlikely to make more than 2000 daily contacts. The United States can be thought of as being made up of many such communities, interconnected by individuals moving among them. Some of these communities are spatial neighbors, connected by people going to work, to malls, or to school. At another level, groups of communities are spatially separated, with people traveling from one community to another. The degree of interconnectivity between communities could affect the rate of smallpox spread on a large scale. More complex networks of communities also enable more choices for the initial introduction of infection. The initial infective persons could be introduced within just one community or be spread out over several communities. Alternatively, the initial infective persons themselves could move among communities. Further research on the interconnectivity of communities and its explicit inclusion in future models, as well as on different modes of introduction of smallpox, is needed and could alter some of the substantive findings presented here. Further research on a larger scale could include an examination of whether targeted vaccination has an advantage in that it would allow focused vaccination in areas where epidemics occur, rather than mass vaccination across the entire United States.

The spread of smallpox within communities depends on (i) the structure assumed within each community and (ii) how much transmission occurs through close versus casual contact. The more identifiable structure there is in the community, the more effective targeted vaccination will be in comparison to mass vaccination. Heterogeneous models generally have slower epidemics with lower final attack rates, as compared to homogeneous models with comparable R_0 values. Although the schools in the United States are on average larger than the schools in our simulations, the age distribution of the population, based on U.S. Census 2000 (*9*), determined the size of the simulated schools. Larger close contact groups could enable the maximum number of secondary cases to be larger than that in our simulations. However, if the schools were larger, our simulator could break them into classrooms, corresponding again to smaller contact groups. Other close contact groups, such as workplaces, could be included.

An important area of uncertainty is how much higher transmission probabilities are in identifiable contact groups than in the community at large. Henderson and Yekpe wrote that "the observed behavior of smallpox in this epidemic suggests that transmission occurring from casual contact is a rare event . . ." [(*20*), p. 423]. In our simulator, the decreasing gradient of transmission probabilities over households and schools, then neighborhoods and communities, reflects the general thought that smallpox is not transmitted effectively by casual contact in the streets or subways, but rather through close contact. Because the close contact groups are known in these simulations, targeted vaccination can be more efficient in our model than in homogeneous models (*5*). Further research could calibrate our model with different gradients of transmission probabilities. As more transmission is assumed to occur in the community at large rather than in close contact groups, our simulated communities would approach random mixing. The higher the proportion of transmission attributed to the identifiable contact groups, the more effective the targeted strategy will be in relation to mass vaccination. Better statistical analysis of available data could provide improved estimates of the relative importance of close versus casual contact in smallpox transmission.

Better understanding of the immune protection (against infection, disease, and infectiousness) provided by both fresh and old vaccinations is required. For example, because assumed residual immunity in vaccinated adults improved the effectiveness of interventions in our model, better knowledge of the protection afforded by vaccination received before 1972 is important. Fresh vaccination of increased numbers of first responders and voluntary vaccination could help prevent secondary spread and increase the effectiveness of postattack intervention. It could also make targeted vaccination competitive with mass vaccination in both preventing and containing a deliberate introduction of smallpox.

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22. This research was partially funded by the Fogarty International Center and NIH grant R01-AI32042. We thank E. McKenzie for initiating this project.

Supporting Online Material
www.sciencemag.org/cgi/content/full/298/5597/1428/DC1
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4 June 2002; accepted 9 October 2002

Viral IL-6–Induced Cell Proliferation and Immune Evasion of Interferon Activity

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Lymphoma cells infected with Kaposi's sarcoma–associated herpesvirus are autocrine dependent on virus-derived interleukin-6 (IL-6), but not on cellular IL-6. During viral infection, host cells induce the antiviral factor interferon (IFN) to up-regulate p21, initiate cell cycle arrest, and inhibit virus replication. Viral IL-6, however, blocks IFN signaling. A viral transcriptional program exists in which only the viral IL-6 gene is directly activated by IFN-α, allowing the virus to modify its cellular environment by sensing and responding to levels of intracellular IFN signaling. The human cytokine cannot mimic this effect because IFN-α down-regulates the IL-6 receptor, gp80. Viral IL-6 bypasses the gp80 regulatory checkpoint by binding directly to the gp130 transducer molecule, resulting in tumor cell autocrine dependence on the viral cytokine for proliferation and survival.

Viral inhibition of host defenses has been linked to the proliferative properties of some virus-infected tumors, because of the overlapping nature of immune and tumor-suppressor signaling pathways (*1*). Kaposi's sarcoma herpesvirus (KSHV) is a non-integrated, episomal DNA virus possessing a virus-derived cytokine, vIL-6, that is expressed in infected primary effusion lymphoma (PEL) cells (*2–4*). These cells become autocrine dependent on vIL-6 but not on the human cell–derived cytokine hIL-6 (*5*), a B cell proliferation factor. In the absence of vIL-6 or when vIL-6 signaling is blocked, these autocrine-dependent cells stop dividing and undergo apoptosis. vIL-6 induces B cell proliferation and contributes to in vitro cell transformation, and thus may play a critical role in KSHV-related hematopoietic tumors such as PEL and multicentric Castleman's disease (CD) (*6–8*). It probably does not appreciably contribute to Kaposi's sarcoma (KS), in which alternative viral transcription programs are operative, because vIL-6 is variably expressed in this endothelial cell tumor.

The reasons why a human cell would become dependent on an exogenous, virus-derived, IL-6–like cytokine are puzzling. Despite intensive study, no major differences in downstream signaling have been found for vIL-6 and hIL-6 (*9*, *10*). The viral and human cytokines, however, differ in their receptor interactions. hIL-6 binds to a specific receptor, gp80, which forms a complex with the transmembrane gp130 transducer molecule responsible for carrying the IL-6 signal across plasma membranes (*11*). Unlike hIL-6, vIL-6 directly engages gp130, but once gp130 is activated, downstream signaling for the two cytokines is similar (*12–14*).

We hypothesized that KSHV-infected cells would become autocrine dependent on vIL-6 if the viral cytokine protects cells against innate immune defenses triggered by viral infection. Interferons (IFNs) are cytokines induced during viral infection to generate an antiviral cellular state and can initiate cell type–dependent growth arrest and apoptosis (*15*, *16*). Under low-serum conditions,

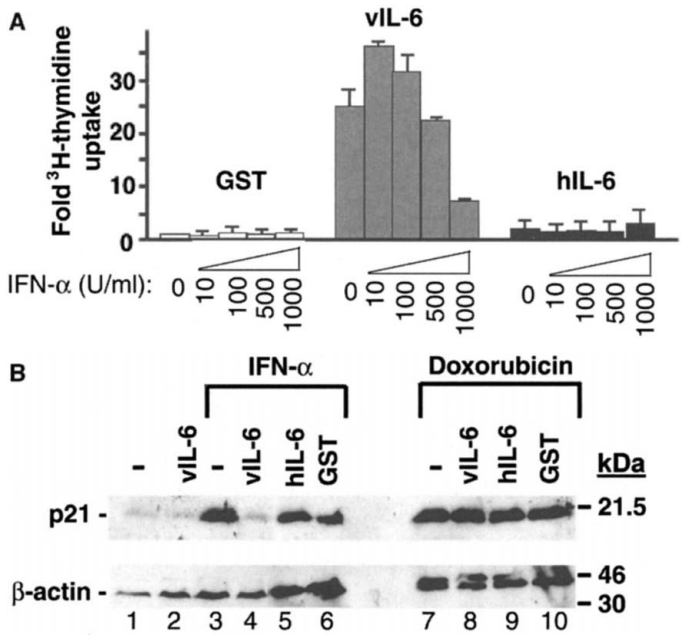

Fig. 1. vIL-6 inhibits the cytostatic effects of IFN-α on KSHV-infected PEL cells. **(A)** vIL-6 but not hIL-6 allows BCP-1 cell proliferation ([^3H]thymidine uptake) in low-serum media in the presence of IFN-α. Recombinant vIL-6, hIL-6, or GST was added to culture media at 100 ng/ml with cells harvested after 48 hours. **(B)** vIL-6 inhibits IFN-α–dependent but not p53-dependent up-regulation of the $p21^{CIP1/WAF1}$ cyclin-dependent kinase inhibitor. $p21^{CIP1/WAF1}$ immunoblotting was performed on BCP-1 cells after 16 hours of vIL-6, hIL-6, or GST treatment (100 ng/ml each) together with 500 IU of IFN-α or 0.4 M doxorubicin. IFN-α induces $p21^{CIP1/WAF1}$ protein expression (lane 3) that is antagonized by vIL-6 (lane 4) but not by hIL-6 (lane 5) or GST (lane 6). $p21^{CIP1/WAF1}$ protein induced by 0.4 M doxorubicin is unaffected on addition of exogenous cytokines or GST (lanes 7 to 10). β-actin is shown for loading comparison.

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