Vaccines and their impact on the control of disease

Angela R McLean

Institute for Animal Health, Newbury, Berkshire, UK and The Wellcome Trust Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, Oxford, UK

Disease control exerts evolutionary pressures that can lead to the evolution of resistance. This has been seen in a spectacular fashion in the evolution of resistance to antibiotics, anti-virals and anti-parasitics. Despite intense (and often successful) attempts to control infectious diseases through vaccination, there is still rather little evidence of the emergence of strains of pathogen resistant to vaccines. This chapter asks why this should be so and what are the exceptions indicating that the evolution of vaccine resistance, though currently rare, is a possibility that should be planned for.

Past success of vaccines

After a carefully orchestrated and long-fought battle run by the World Health Organization, smallpox was eradicated in 1979. This success lead to optimism that other important diseases of childhood could also be eradicated through vaccination. But despite the availability of cheap, safe, and effective vaccines, no other pathogen has yet been eradicated on a global scale. Nonetheless, vaccination has pushed a number of childhood infectious diseases to the verge of extinction without their associated pathogens adapting to circumvent this evolutionary pressure. Most vaccines in current use give highly effective, long-term protection against infections of childhood[1]. The agents causing such infections do not exhibit wide antigenic variation. It will be argued here that such vaccines, by closely mimicking naturally acquired immunity, exploit the same biological constraints that prevent the pathogens from re-infecting people with naturally acquired immunity. In other words, childhood infectious diseases are precisely those in which it is possible to mount an immune response that the pathogen cannot circumvent, thus people only get the disease once. From the point of view of the evolution of vaccine resistance, they are the easy targets. All that vaccine induced immunity has to achieve is to get 'close enough' to natural immunity – in terms of

Correspondence to Dr Angela R McLean, Institute for Animal Health, Compton, Newbury, Berkshire RG20 7NN, UK

degree of protection and degree of cross reactivity – and existing constraints on the pathogen's evolution can allow control without the emergence of resistance.

Future hopes for vaccines

Until quite recently most theoretical work on vaccine effectiveness assumed that a vaccine is equally efficacious against all existing strains of an infectious agent[2]. For pathogens with rich strain structure this is often patently not the case. Even before vaccination has acted to shift the competitive balance between strains, it is clear that the vaccine will give better protection against some strains than others. In such a situation one would like to ask about the changes in incidence of infection with different strains subsequent to vaccination[3–5]. Since the strain structure is apparent before vaccination, it is also interesting to ask what would be the best way to design vaccines against such infectious agents. Is it best to target just one strain or is cross-reactivity the all-important goal in vaccine design? Theoretical work on such questions has been moving ahead rapidly in recent years, and in this chapter some of the general results emerging from that theory are presented.

Community level impact of vaccines

The basic reproductive rate and vaccine effectiveness

In considering the community-level impact of vaccines it is useful to introduce the vaccinated reproductive rate R_0. This represents the number of secondary cases caused by one infectious individual introduced into a community where everybody is susceptible. R_0 can be generalised to R_p, the number of secondary cases caused by one infectious individual introduced into a community where a fraction p have been vaccinated and everybody else is susceptible. The eradication criterion for an infectious agent is derived by calculating the vaccination

Table 1

Infection	Location	Date	R_0	p_c
Measles	UK	1950s	15	93%
Measles	Senegal	1964	18	94%
Smallpox	India	1960s	4	75%
Polio	USA	1955	6	83%

coverage (p_c) at which R_p becomes smaller than one. The larger R_o, the more difficult it is to eradicate an infectious disease[2,6]. R_o can be calculated from age stratified incidence or serological data and thus p_c can be inferred. Comparing values of R_o and p_c for different infectious diseases in different settings (Table 1) it is easy to see why smallpox has gone, polio is going and measles is still with us.

The honeymoon period

The non-linear nature of host–parasite interactions can lead to non-intuitive responses to apparently straight-forward interventions. One of these is the 'honeymoon period', the period of very low incidence immediately following the introduction of a mass vaccination programme. This happens because susceptibles accumulate much more slowly in a vaccinated community, so it takes a long time to reach the threshold number required for an epidemic[7,8]. Such patterns were predicted using mathematical models in the 1980s and have since been observed in communities in Asia, Africa and South America[1,9–11].

Competition, an inevitable consequence of cross reactivity

Directly transmitted infectious diseases are obligate parasites of their hosts; for them, hosts are a substrate over which they must compete, either for internal resources or to avoid immune recognition. Any two pathogens that share cross reacting epitopes are inevitably in competition to be the first to infect susceptible hosts. When the pathogen has strongly immunogenic conserved epitopes, competition can lead to the simple dominance of a single strain. The dominant strain will be the one with the largest basic reproductive rate R_o. But, when conserved epitopes are only weakly immunogenic, competition can result in a shifting balance of strains with complex antigenic structure[12,13].

The emergence of vaccine resistant strains

What might happen when vaccination is imposed upon such competitive interactions? Consider a simple case where a single strain of pathogen circulates before vaccination. Suppose that strain constantly generates less fit (*i.e.* lower Ro) mutants, some of which are vaccine escape mutants. In the absence of vaccination, a vaccine resistant strain would be outcompeted if it had a lower R_o than the wild-type. Vaccination acts to shift the competitive balance between wild-type and resistant strains.

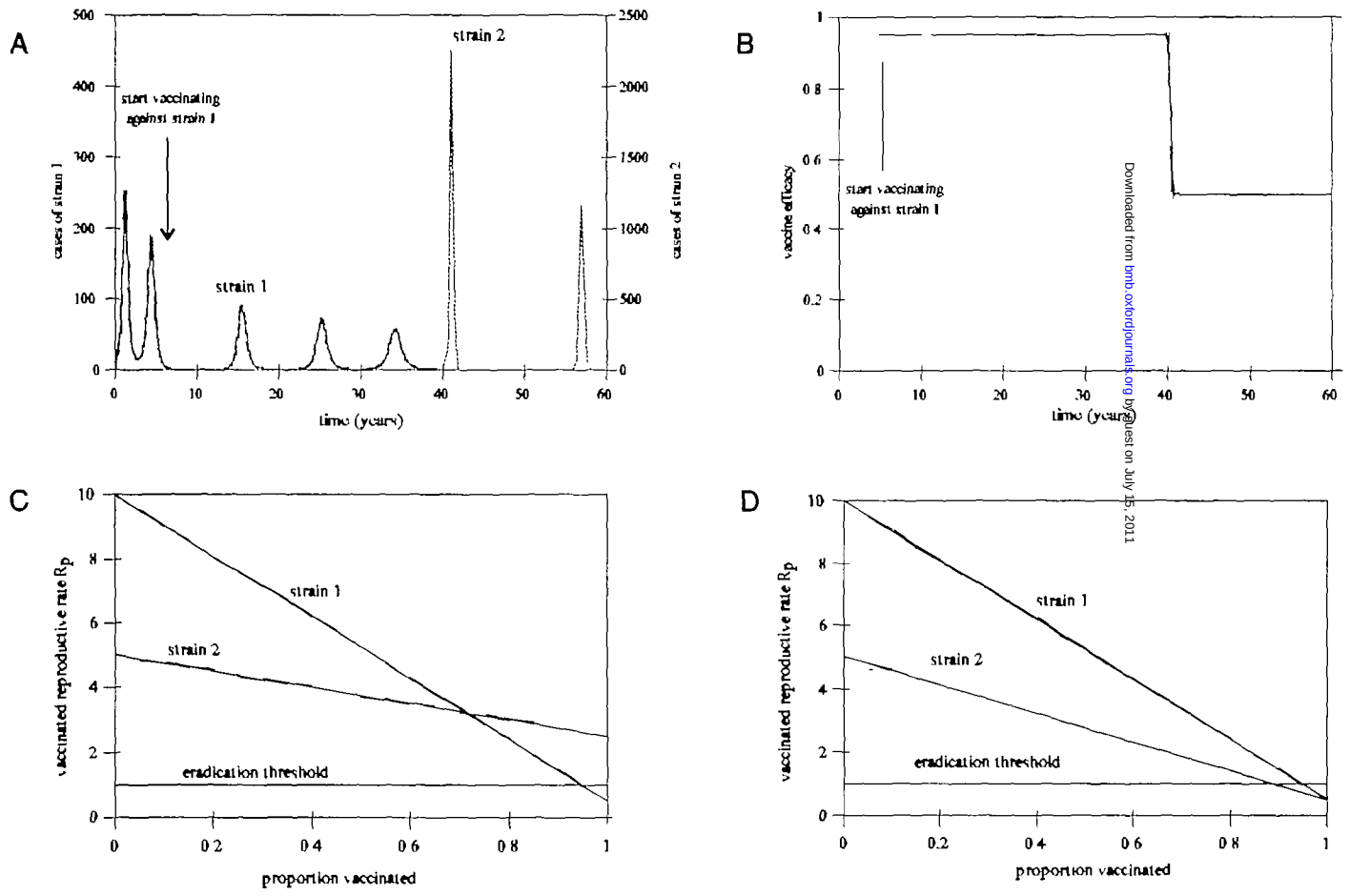

Fig. 1 *Emergence of a vaccine resistant strain.* **(A)** *At time 3 years, a vaccination campaign is introduced that reaches 80% of newborns The vaccine is 95% efficacious against the circulating strain (strain 1) but only 50% effective against the vaccine resistant strain (strain 2). A 10 year honeymoon period ensues followed by post-honeymoon outbreaks of strain 1. Almost 40 years after introduction of vaccination, there is an outbreak of the vaccine resistant strain.* **(B)** *During the post-honeymoon outbreaks vaccine efficacy is unchanged. These outbreaks are a natural consequence of the non-linear nature of interactions between susceptible and infectious individuals. At time 40 years, when strain 2 emerges, vaccine efficacy falls from 95% to 50% signalling the arrival of the new strain.* **(C,D)** *Vaccinated reproductive rates predict the outcome of competition under different vaccination regimens The strain with the higher vaccinated reproductive rate will eventually dominate* **(C)** *Vaccine with low cross reactivity. At high vaccination coverage, the vaccine resistant strain has the competitive advantage.* **(D)** *Vaccine with high cross-reactivity. If a vaccine is so cross-reactive that the vaccine resistant strain only gains competitive advantage at coverage levels above that at which wild-type is eradicated, vaccine resistant strains can never emerge*

If vaccine induced immunity is less cross-reactive than naturally acquired immunity, there may be a level of vaccine coverage above which a vaccine resistant strain will emerge as a result of the vaccination campaign. This situation is illustrated in Figure 1A. Vaccination begins at time 3 years. There follows a period of very low incidence (the honeymoon period) before epidemics of the wild-type strain restart[7]. Notice (Fig. 1B) that vaccine efficacy remains at 80% during these post-honeymoon epidemics. The post honeymoon epidemic that starts at time 15 years is a result of the slow accumulation of unvaccinated susceptibles. A small number of those who have been vaccinated are also infected because of the incomplete protection conferred by the vaccine. Several decades later, a much larger epidemic occurs and at the same time vaccine efficacy plummets. The vaccine resistant strain has achieved competitive dominance as a result of the growing number of vaccinated individuals. These vaccinated people are well protected against wild-type strain, but have only minimal protection against the vaccine resistant strain. The vaccinated reproductive rate for the vaccine resistant strain is larger than that for the wild-type strain. It takes several decades of accumulation of vaccinated people before this shift in competitive advantage manifests itself in epidemics of the vaccine resistant strain but, for this combination of parameters, the effect is inevitable. It is not, however, an unavoidable consequence of vaccination. Highly cross-reactive and immunogenic vaccines can lead to the eradication of both strains at coverage levels below those at which the vaccine resistant strain gains the competitive advantage. Alternatively, low levels of vaccination leave the wild-type strain the competitive superior. Figure 1C,D illustrates these possibilities with plots of the vaccinated reproductive rate, R_p, against proportion vaccinated, p. Figure 1C has the same parameter values as Figure 1A. The vaccine is only weakly immunogenic against the vaccine resistant strain, the vaccinated reproductive rate, R_p, for the vaccine resistant strain falls rather slowly with increasing proportion vaccinated. With 80% vaccination coverage R_p for the vaccine resistant strain is greater than R_p for the wild-type strain, so it is inevitable that there will eventually be an outbreak of the vaccine resistant strain. If vaccination coverage had been much lower, the vaccine resistant strain would never have gained the competitive advantage. A vaccine with greater cross reactivity will not face these problems. Figure 1D illustrates an example where both strains would be eliminated before the vaccine resistant strain gained the competitive advantage.

Thus, there are three possible explanations why we have not seen outbreaks of vaccine resistance in response to the major vaccination campaigns against childhood infectious diseases. The first (Fig. 1A) is that we haven't – yet. The second (Fig. 1C) is that vaccine coverage is too low to give the competitive advantage to resistant strains. The third

(Fig. 1D) is that current vaccines give enough cross-immunity so that resistant strains will never emerge[3].

Using cross-reacting strains, the virulence antigen hypothesis

In many situations, complex antigenic structure is apparent before vaccination is introduced. These situations have been studied using mathematical models which permit multiple strains to co-exist but allow infection with one strain to make subsequent infection with other strains less likely[3–5]. These cross-protection terms put the strains in competition with each other, so that the prevalence of one strain is affected by the prevalence of the other. Under these circumstances of cross protection, vaccination against one strain can lead to increasing prevalence of the other[3–5]. Ewald[14] has suggested that there are circumstances where these competitive interactions amongst strains can be exploited with a strategy named anti-virulence vaccines. Suppose two strains circulate and strain 1 is highly virulent whilst strain 2 is less so. A vaccine that is purely targeted at strain 1 with no protection against strain 2 will have both a direct and an indirect method of reducing infections with the virulent strain. First of all, those successfully vaccinated against strain 1 will be safe from infection with the virulent form. They remain susceptible to infection with strain 2, the avirulent form, and prevalence of strain 2 therefore increases, leading to further infection of susceptibles with strain 2. The cross-protection afforded by strain 2 means that these people too are protected from infection with the virulent strain. This is the effect of free vaccination that Ewald refers to, and is clearly an added benefit of a vaccine targeted at virulent strains. It has been suggested that this effect is so valuable that cross-reacting components (which protect against both strains) should be excluded from vaccine preparations. However, given the complexity of the competitive interactions between strains and their response to vaccination, this is a claim that requires careful quantitative investigation.

Examples

This chapter has investigated two different scenarios in which vaccine escape mutants might arise. The first is for monotypic pathogens in which the vaccine escape mutant would be an entirely new variant, not observed before the introduction of vaccination. The conclusion is that, so long as vaccines continue to exploit the opportunities for broad cross-reactivity offered by the biology of such pathogens, the emergence of vaccine escape mutants is unlikely. The second scenario is when rich strain structure exists before vaccination is introduced. In this case, any

vaccine that targets only a subset of the strains already observed is predicted to lead to increased circulation of the untargeted strains. This is because the removal of competing strains by the vaccine leaves an opportunity for increased circulation of the untargeted strains. A third possibility, not discussed in the context of the models, is that a pathogen may start to exploit susceptible hosts after eradication of a competing infection and subsequent cessation of vaccination. Whilst dealing with large numbers of eradicated pathogens is not yet our problem, it seems worthwhile to consider the possibility that vaccination will have to continue post-eradication in order to prevent infection with antigenically related zoonoses.

Measles, why no resistance yet?

A comparison of the sequences of currently circulating measles virus with historical samples shows that there has been an increase in the rate of nucleotide change in the measles haemagglutinin gene since vaccination became widespread[15]. Furthermore, this sequence variation translates into antigenic differences between currently circulating strains and the strains that make up the vaccine[16]. Serum from individuals infected with current wild-type strains reacts 4–5-fold more effectively with wild-type strains than it does with the vaccine strain. Fortunately, the reverse is not true, serum from people who have recently been vaccinated have equally strong antibody response to either the strain they were vaccinated with, or current wild-type strains. Thus, for the moment, there is no evidence that measles vaccine escape mutants are about to emerge.

Hepatitis B, will vaccine resistant strains spread?

Antigenic subtypes of hepatitis B occur naturally, and Hepatitis B vaccine escape mutants have been identified[17,18]. Since the vaccine is relatively new, there is no large pool of vaccine recipients to act as fuel for an epidemic of vaccine-resistant hepatitis B. However, as the number of people vaccinated against hepatitis B grows, the transmission of the variant hepatitis B virus must be considered. It is already being suggested that the variant sequence should be included in future vaccines.

Pertussis in The Netherlands

The Netherlands had an effective pertussis control programme in place. In the years 1989–1995, the annual number of reported cases ran at

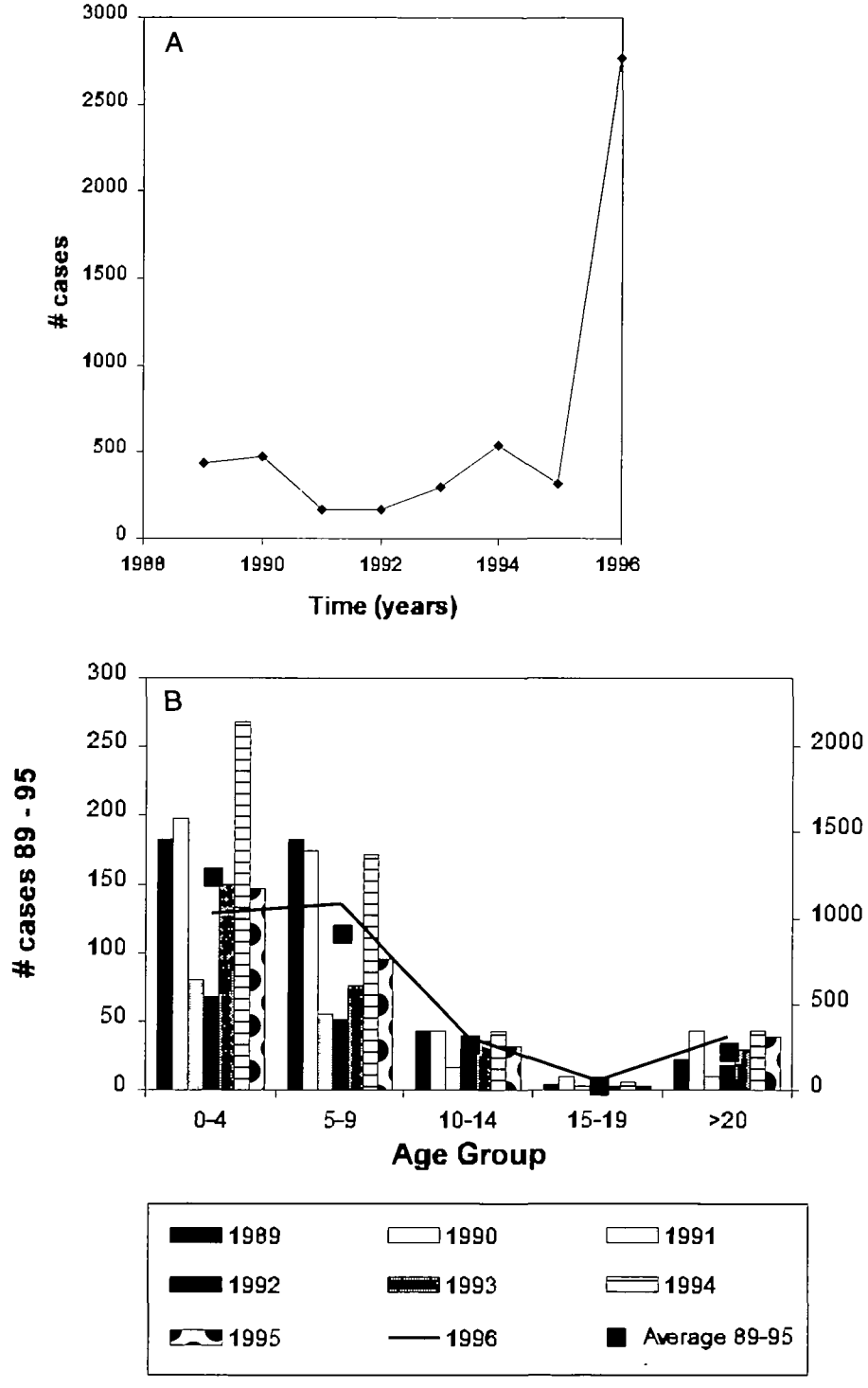

Fig. 2 Pertussis outbreak in The Netherlands **(A)** After many years of low incidence, in 1996 The Netherlands experienced a major outbreak of reported cases of pertussis. **(B)** The age distribution of cases in the outbreak was indistinguishable from that of earlier years.

under 500. Then, in the summer of 1996, there was a pertussis outbreak and, in the year as a whole, over 2500 cases were reported (Fig. 2A). There was no discernible shift in the age distribution of cases. A post-honeymoon period epidemic would have a clear signature of an increase in the average age at infection – after 7 years' low incidence this would have been large enough to discern even with cases reported in 5 year age bands. It has been suggested, but not yet confirmed, that the resurgence of pertussis is due to the emergence of strains of *Bordetella pertussis* less sensitive to the immune protection provided by the vaccine[19–21].

Smallpox and monkeypox, a rare problem

The eradication of smallpox and consequent cessation of vaccinia vaccination is often held up as the holy grail of goals for vaccine strategies. As pointed out by Aaby[22], vaccination has poorly understood, but quantifiable, benefits over and above the prevention of infection. There is a further reason why one might consider continuing with vaccination even after eradication of an infectious agent. The patterns of competition amongst strains discussed in this section applies to any group of infectious agents that share cross-reactive antigens – not just different strains of the same pathogen. Monkeypox, smallpox and vaccinia give an intriguing example. Before the eradication of smallpox, infection of humans with monkeypox virus was rare, and human-to-human transmission rarer still. Vaccinia immunisation protects against monkeypox virus infection, and so, presumably, did immunity to smallpox. A recent outbreak of monkeypox virus in Zaire was characterised by large numbers of human cases (mostly amongst smallpox naive individuals) and long chains of human-to-human transmission. Thus, it may be that first smallpox infection and then vaccinia immunisation were protecting exposed individuals from infection with monkeypox virus. Now that smallpox has been eradicated, and vaccination has ceased, a pool of individuals susceptible to monkeypox virus infection has accumulated and appears to have fuelled an epidemic. Re-introduction of vaccinia immunisation is being considered[23,24].

Strategies for continued success with vaccines

What impact will a vaccine have when deployed in a community? Whilst a vaccine's efficacy represents the protection an individual can expect following immunisation, a vaccine's effectiveness is a broader measure of its benefits for whole communities. Effectiveness certainly includes efficacy, but also encompasses the long-term efficacy of a vaccine

(beyond that measured in conventional efficacy trials), secondary effects of vaccination, and the impact of vaccinating against one strain upon cross-reacting strains (as discussed below).

Duration of protection

Simple calculations reveal that the community-level impact of a vaccine is extremely sensitive to the duration of protection that the vaccine endows. The relevant measure of duration is not the rate or half-life of decay of vaccine induced protection, but the fractional reduction in life-time susceptibility to infection. An example: suppose an individual would be at risk for HIV infection for the whole of a 40 year sexual career. A vaccine that gives perfect protection in all recipients that lasts on average for 10 years has the same effectiveness at the community level as a vaccine that gives life-long protection but only works in one-quarter of the people who receive it. Thus long-term vaccine induced protection is a crucial element of a vaccine's effectiveness. The usual duration of a vaccine efficacy trial is 2 or 3 years. Given the importance of long-term efficacy, long-term follow-up of cohorts involved in vaccine trials is clearly essential.

Breadth versus depth for vaccine efficacy

Theoretical models that combine epidemiology and evolutionary biology have been used to investigate how vaccination could act to shift the competitive balance between two strains of an infectious agent[3–5,26]. A recurring theme that comes from several different models is that breadth of effect, *i.e.* great cross-reactivity is an extremely important feature of a successful vaccine, even if this breadth is achieved at the cost of efficacy. Live or whole-killed vaccines have, for decades, been using a kind of multi-drug therapy that may have prevented the emergence of resistant strains. It would be ironic if, just at the moment that multiple therapy with drugs is recognised as the only way to overcome drug resistance, a switch to vaccines with just a few epitopes were to lead to escalating problems in vaccine resistance.

Conclusions

Vaccines have been a hugely successful technology for controlling infectious diseases in the past. Great hopes are pinned upon their use in ever broader applications in the future. Many vaccines in widespread

use are rather low-tech preparations of live-attenuated or whole-killed pathogens. These have inherited properties of endowing broadly cross-reactive and long-lasting immunity, properties that have probably been of extreme importance to the successes that have been seen in the past. These are properties that new vaccines will have to emulate if they are to repeat the successes of the past.

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