



## Editorial

## The re-emergence of measles in developed countries: Time to develop the next-generation measles vaccines?

Measles is the most transmissible infectious disease known in humans, and remains one of the top causes of death in children worldwide. Even in highly developed countries, measles kills approximately three of every 1000 persons infected. While no treatment exists for measles, prevention in the form of vaccination has been available since the 1960s. Despite the significant global morbidity and mortality of measles, considerable progress is evident. Just a decade ago, in 2000, measles killed an estimated 777,000 people a year worldwide. In 2010, measles killed only 160,000 worldwide—a testament to widespread use of vaccine.

But concerns lurk, unnoticed for the most part. Despite the aforementioned gains measles is re-emerging as a serious public health threat, and outbreaks are occurring even in highly developed countries where vaccine access, public health infrastructure, and health literacy are not significant issues. This is unexpected and a worrisome harbinger—measles outbreaks are occurring where they are least expected. As illustrated in [Table 1](#), since 2005 these outbreaks have also occurred in the U.S. – with surprising numbers of cases occurring in persons who previously received one or even two documented doses of measles-containing vaccine. In fact, as of September 2011, the U.S. has had 15 measles outbreaks with 211 confirmed cases—the highest number of cases since 1996 [1,2].

Large measles outbreaks are also occurring in many other developed countries [3–6]. Thirty-three European countries have reported outbreaks of measles this year [5] with more than 30,000 known cases [4]. The UK has declared measles once again endemic [3]. In the first seven months of 2011, France alone suffered 14,025 cases of measles, and Spain has reported 1777 cases [7]. In none of these countries are vaccine access, nor health care infrastructure, serious issues. Where data exist, such outbreaks result from both failure to vaccinate, and vaccine failure.

Failure to vaccinate is a serious socio-cultural issue, and significantly hampers public health goals. Measles immunization rates, particularly in certain areas of the U.S. and western Europe, have plateaued or decreased and experts suspect this is a result of the now-debunked notion that measles vaccine caused autism—a false claim that adversely influenced MMR vaccination choices among a generation of parents. In addition, few current parents have any direct experience with measles and are uninformed about its infectivity, morbidity, and mortality. Because measles outbreaks have occurred in scattered areas of the country, the average parent is unaware of the danger, and feels no urgency to respond by immunizing their children—thus further enlarging the pool of susceptibles.

Receiving less attention, however, is the issue of vaccine failure. While the current vaccine is acknowledged as a good vaccine, we and others have demonstrated that the immune response to measles vaccine varies substantially in actual field use. Multiple studies demonstrate that 2–10% of those immunized with two doses of measles vaccine fail to develop protective antibody levels, and that immunity can wane over time and result in infection (so-called secondary vaccine failure) when the individual is exposed to measles. For example, during the 1989–1991 U.S. measles outbreaks 20–40% of the individuals affected had been previously immunized with one to two doses of vaccine. In an October 2011 outbreak in Canada, over 50% of the 98 individuals had received two doses of measles vaccine. [Table 1](#) shows that this phenomenon continues to play a role in measles outbreaks. Thus, measles outbreaks also occur even among highly vaccinated populations because of primary and secondary vaccine failure, which results in gradually larger pools of susceptible persons and outbreaks once measles is introduced [8]. This leads to a paradoxical situation whereby measles in highly immunized societies occurs primarily among those previously immunized [8].

The WHO and others have called for both country or region-specific elimination and global eradication of measles [9]. However, eradication (complete elimination of the global spread and transmission) of measles is unlikely as modeling studies suggest that herd immunity of approximately 95% or greater is required to eliminate persisting measles endemicity [10]. Because field studies demonstrated evidence of primary vaccine failure and population-levels of immunity below this threshold, the U.S., like many other countries, adopted a two-dose measles vaccination policy in the early 1990s. However, even with two documented doses of measles vaccine, our laboratory demonstrated that 8.9% of 763 healthy children immunized a mean of 7.4 years earlier lacked protective levels of circulating measles-specific neutralizing antibodies [11], suggesting that even two doses of the current vaccine may be insufficient at the population level.

Thus, while an excellent vaccine, a dilemma remains. As previously mentioned, measles is extraordinarily transmissible. At the same time, measles vaccine has a failure rate measured in a variety of studies at 2–10%, and modeling studies suggest that herd immunity to measles requires approximately 95% or better of the population to be immune [12]. It remains then an open question as to whether the current vaccine is sufficiently immunogenic and efficacious to allow eradication—even though measles can be controlled, and even eliminated in some regions for defined periods of time. Whether elimination can, in fact, be sustained is unknown,

**Table 1**  
Recent measles cases in US as of September 15, 2011.

Year	Total infected	Unknown vaccine status	No doses of measles vaccine	Received only 1 dose	Received 2 doses	Any dose where known
2005	66	8	50	7	1	13.8%
2006	55	15	25	12	3	37.5%
2007	43	10	25	4	4	24.2%
2008	140	21	108	6	5	9.2%
2009	71	15	49	6	1	12.5%
2010	63	20	37	2	4	14.0%
2011	211	48	134	16	13	17.8%

Source: Div Viral Diseases, Epi Branch, Natl Ctr Immunization & Resp Dis, CDC, September 21, 2011.

as it has not been evident over sufficiently long periods of time (decades) across geographic regions.

Other limitations of the vaccine should also be acknowledged and raise concern in terms of the current vaccine's utility in eradication efforts [13–16]. Practical limitations of the vaccine are that it cannot be administered to those who are immunocompromised, who have allergies to vaccine components, or who are pregnant. Additional limitations are the need for a cold-chain, the need for trained health care personnel to administer vaccine, and the need to delay immunization until 12 months of age due to passively transferred maternal immunity. Socio-cultural limitations are also extremely important, and often either overlooked by the architects of elimination and eradication efforts, or unexpectedly arise due to temporal trends. Primary among these are that surprising numbers of otherwise well educated people reject the vaccine due to safety fears—effectively diminishing its worth as a public health tool. Thus, current measles vaccines can only be used to protect individuals without contraindications, and those willing to accept the vaccine, which are conditions that leave a large enough segment of the population susceptible and unprotected from measles such that cases will continue to occur.

The practical answer to the dilemma of measles re-emergence is the development of better, next-generation vaccines. Given recent public opinion and large numbers of parents rejecting the current vaccine, combined with practical and immunologic limitations, new vaccines appear to be necessary. The ideal vaccine would require only one dose to be given at or soon after birth; it would lack contraindications and permit administration without highly trained health care personnel; it would be inexpensive, and heat stable. Next-generation vaccines such as peptide-based subunit vaccines, perhaps with adjuvants, DNA vaccines, aerosol vaccines, and other approaches are possible, and active research is ongoing. Such next-generation vaccines could achieve the goal of measles eradication if such vaccines are more immunogenic than current vaccines, result in extremely high rates of protective immunity stable over a lifetime, and are widely accepted by the populace.

To date, despite multiple efforts, the reality is that for the practical, socio-cultural, and immunologic reasons outlined above, we have not eradicated measles. As a result, measles is re-emerging as a public health threat, and our current tool for prevention has limitations that increasingly look to be significant enough that sustained elimination, much less eradication, is unlikely. Perhaps it is time to consider, in earnest, the development of the next generation of measles vaccines.

## Disclosures

Dr. Poland chairs data monitoring committees for non-measles vaccines being developed by Merck & Co. Dr. Jacobson also serves

on a data monitoring committee as well as a safety review committee concerning non-measles vaccines produced by Merck & Co.

## Acknowledgement

This work is supported in part by funding from the National Institutes of Health, AI-033144.

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