removal of uracil with a bacteriophage peptide (ugi) that inactivates the cellular repair enzyme uracil glycosylase, mutation frequencies are enhanced to levels that obviate the need for additional selection (see the figure). The sequence of such targeted yeast genomes contains negligible off-target changes, but up to 10% localized mutation. By using rat APOBEC1, a stronger DNA-RNA deaminase than lamprey PmCDA1 (*8*), Komor *et al.* obtained mutation frequencies up to 20% in human cells, with a further increase to 37% achieved by biasing the cellular mismatch repair toward correction of the unedited DNA strand—at the slight cost of increasing indels (from <0.1 to 1.1%). APOBEC1, like the related human APOBEC3 deaminases, is a powerful genome mutator in cancer cells (*9*, *10*), and even in physiological conditions, AID off-target activity is a frequent cause of oncogenic mutations and translocations (*11*).

"With localized mutagenesis...comes the promise of gene correction..."

Although testing known off-target sites of CRISPR-Cas9 for APOBEC-dependent mutations in the study of Komor *et al.* suggests low collateral damage, whole-genome or -exome sequencing will still be a necessary proposition for human gene therapy. Physically tethering the deaminase to Cas9 might be the key strategy that allows both groups to minimize unwanted editing activity in mammalian cells, where transient single-stranded DNA is unavoidably associated with transcription. It could well be that "less is more" in this case and that the less efficient deaminase AID might be a better choice in mammalian cells.

Transient use of dCas9-PmCDA1-ugi practically eliminates off-target mutations and indels but limits the genes amenable for correction because only transitions from GC to AT pairs can be reliably achieved. This is not a major limitation to technological applications; the obvious combination of dCas9-AID with yeast display immediately comes to mind as a tool for accelerated antibody evolution, but many other examples are ripe for its use, from genome evolution to conventional genetics.

Aside from the technical innovation, the methods described by Nishida *et al.* and Komor *et al.* could provide insights into the physiology of these deaminases. Coexpression of dCas9 and PmCDA1 is sufficient to increase the frequency of localized mutation even in trans; indeed, the main requirement for deamination is the presence of a small but persistent single-stranded region of DNA (*12*). In vivo, other factors contribute to editing efficiency, such as the sequence context preferences of the edited cytosine and its position within the open DNA. In both the Nishida *et al.* and Komor *et al.* studies, distal sites were more frequently edited, a difference that was exacerbated for cytosines that did not fall within the sequence consensus of the deaminase. As exemplified by Nishida *et al.*, a more relaxed sequence context favored by AID [WRC (where W is either A or T, and R is either A or G) versus NTC (where N is any base)] can be an advantage for mutagenesis applications, whereas hybrid deaminases with different sequence context preferences could be part of the targeted mutation toolkit (*13*).

Although powerful, the system is still short of the promised targeted base editing. One reason is that mutations are biased to GC pairs and are promiscuous within the single-stranded bubble created by the Cas9-RNA guide. More importantly, the short homology required for RNA-guided recognition is an adaptation that provides bacterial CRISPR defense the flexibility to accumulate immunity against a large number of viruses or foreign plasmids while retaining a compact genome, but results in promiscuous targeting in larger genomes. As in the case of the deaminase component, a less efficient Cas9 with a more fastidious and longer homology requirement would be a desirable development.

Harnessing mutation, a dream long anticipated by geneticists and pioneered by early molecular biologists, was still haunting Michael Smith in his 1993 Nobel Prize lecture: "The ignis fatuus of genetics has been the specific mutagen, the reagent that would penetrate to a given gene, recognize it, and modify it in a specific way." He was quoting Joshua Lederberg's 1959 Nobel Prize lecture. By the looks of it, the dreamt future of genetics is now. ■

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VACCINES

Vaccine trust and the limits of information

Understanding trust in local contexts is key to communication about vaccination

By **Heidi J. Larson**

Over the past decade, there has been growing recognition and increasing research around the phenomenon of vaccine reluctance and refusal (*1, 2*). More recently, there has been a flurry of articles on what is being referred to as "vaccine hesitancy," depolarizing the earlier characterization of individuals or groups as being outright pro- or antivaccine, and instead recognizing the liminal state between becoming aware of, and deciding whether or not to accept, vaccination. Episodes of waning public confidence around vaccines have become so global that the World Health Organization's Strategic Advisory Group of Experts on Immunization convened a working group (*3*) to better understand and recommend actions to address this growing challenge of vaccine hesitancy, which the group defined as "delay in acceptance or refusal of vaccination despite availability of vaccination services." Indeed, vaccine hesitancy is complex and context specific (*4*). How can we better understand the circumstances that influence this state to ensure more effective uptake of vaccines and secure public health?

Faced with an ever-growing portfolio of new vaccines and combinations of vaccines, parents—and society more broadly—are becoming more questioning as they assess whether vaccines for themselves or their children are too many or too new, better given individually or in combination, or worth even the smallest risk. The landscape of information and misinformation about vaccines, as well as the varied and sometimes divisive views of legitimate and self-espoused experts, is further complicating the public's genuine interest in making the right decision. A broader environment of distrust in institutions (*5*) and "experts" (*6*) additionally prompts pub-

Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. Email: heidi.larson@lshtm.ac.uk

lic questioning, with some trust issues so tense that refusal of health interventions is uncompromising, with little room for reason. For example, this happened in the early days of the West Africa Ebola response when some families in the Ebola-affected countries hid sick family members for fear that they would go to treatment centers and never return. In Guinea, some even resorted to violence against health workers.

Various studies have examined the positive and negative nudges along the increasingly complex path to a vaccination decision, and a number of them point to the importance of trust as a key lever in the decision-making process (*7, 8*). Recent research by Scherer *et al.* (*9*) investigated one of the identified drivers of distrust—lack of trust in vaccine information—which is perceived as being incomplete, inadequately researched, or not fully transparent. Another recent study of 67 countries found that there was overall positive sentiment about the importance of vaccines, but lower confidence reported in the safety of vaccines (*10*). Furthermore, countries with high levels of schooling and good access to health services reported some of lowest confidence in vaccine safety.

Scherer *et al.* explored whether or not providing more information on vaccination against human papilloma virus (HPV) made study participants more confident and willing to accept the vaccine. HPV infections can cause cervical, vaginal, anal, throat, and penile cancers. Vaccination is recommended at ages 11 and 12, when children have a robust immune response. The timing protects individuals before most become sexually active and at risk of exposure to HPV. The study reports on three surveyed groups—one given the standard HPV vaccine information sheet from the U.S. Centers for Disease Control and Prevention (CDC); another presented with the standard sheet supplemented with more information about the Vaccine Adverse Event Reporting System (VAERS) database (which is cosponsored by the CDC and U.S. Food and Drug Administration) and the goals of VAERS in lay language; and a third group shown guidance on how to interpret the cases reported to VAERS as well as a summary of deaths and permanent disabilities reported in 2013. Interestingly, the group given the most information was the least willing to be vaccinated.

However, it is difficult to generalize from the findings of Scherer *et al.* for a number of reasons. One point, which the authors note, is that the U.S. sample that was surveyed was largely white, more educated than the general population, and more conscientious in participating in surveys. Also, and perhaps more important, the group that received the most information also received the least certain information—that is, they received information from VAERS. VAERS is a passive online reporting system where anyone can report a suspected adverse event following immunization, none of which have yet been investigated to confirm whether or not the event was coincidental or caused by the vaccination. As noted on the VAERS website, "The report of an adverse event to VAERS is not documentation that a vaccine caused the event…Reports vary in quality and completeness. They often lack details and sometimes can have information that contains errors" (*11*). Although Scherer *et al.* acknowledge this characteristic of VAERS and, from a trust-building perspective, VAERS is a proactive effort on the part of the government to listen to the concerns of the public, it also risks being misinterpreted. Given that the HPV vaccine is one of the more challenging vaccines in terms of public acceptance (as of 2015, state-level data for three doses of HPV vaccination ranged from 24 to 68% for girls and 16 to 58% for boys) (*12*), it is not surprising that after seeing additional information exposing possible, albeit uncertain, risks, the third group in the study would be less inclined to vaccinate. The results may have been different had the third group received more information than the second group, albeit a type of information that was more complete and less ambiguous.

"Building trust and confidence in those who provide the information and the vaccines, as well as the system that delivers them, is also key."

More information alone, however, does not build trust. As Dempsey *et al.* (*13*) found, "attitudes and life experiences," along with the opinions of their doctor and their peers, were stronger influencers on survey respondents than information. In other research (*5*), trust in the medical profession and in one's personal health care provider, were important. In other words, the source of information matters as much as the content.

Trust is relational, and is often defined as "competence to do what one is trusted to do" (*14*) and also implies trust in the motivations of the trusted. Do they have my—or my child's—best interest in mind?

The issue of motive was writ large in the local anxieties around the Ebola virus outbreak control measures (such as quarantine) and regarding the various stages of the clinical trials of multiple Ebola vaccine candidates. The trust building for both issues was critical to the eventual deployment of both interventions. Siegrist *et al.* (*15*) point to trust as a key lever of public compliance in outbreaks, and it will certainly be key to ongoing Ebola vaccine trials as well as the recently approved start of human trials for Zika vaccine candidates. Understanding the dynamics of existing trust relationships, and building on them, will be essential to support clinical trials as well as eventual deployment of new vaccines. Building trust and confidence in those who provide the information and the vaccines, as well as the system that delivers them, is also key. For example, in India in 2010, women's groups had called for a public forum to discuss HPV vaccination but were ignored for months; this resulted in stronger activism against vaccination, and the program was eventually suspended. In Kenya, the Conference of Catholic Bishops, which had always been an invited partner in national vaccination campaigns, became suspicious when they were initially excluded from the tetanus vaccination campaign, and mobilized resistance in response. Local understanding of trust networks and weak points is required, as well as understanding the key issues that inhibit trust. Only then can genuine trust building begin, allowing for more openness to interventions, even in times of risk and uncertainty. ■

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Heidi J. Larson

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