Since 1918, the association of coinfection with *S aureus* has been a persistent theme in the literature on influenza.[9] Defects in bacterial killing by alveolar macrophages, neutrophil recruitment and function, and T-cell-dependent immune responses predispose the influenza-infected lung to *S aureus* superinfection.[10] In a meta-analysis of studies with enrolment during 1999–2012, the authors found that *S aureus* was the cause of 28% of bacterial coinfections with influenza.[11] In 33 US hospitals in 2013–14, we found that *S aureus* accounted for more than 36% of bacterial coinfections of severe influenza, and was the leading cause of such complications.[12] Aliberti and colleagues did not record which patients had a concordant influenza infection and bacterial community-acquired pneumonia. Influenza coinfection in their study therefore might have been an unaccounted confounding variable biasing the geographic variability reported in the prevalence of *S aureus*.

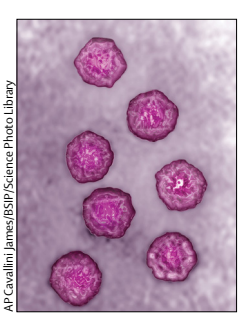
Further research is necessary to delineate the worldwide molecular epidemiology of *S aureus* and MRSA pneumonia and the clinical and microbial risk factors that are responsible for the great disparity in their prevalence noted by Aliberti and colleagues in their impressively large and geographically diverse study.

Michael Z David
Departments of Medicine, Pediatrics, and Public Health Sciences, University of Chicago, Chicago, IL 60637, USA
mdavid@medicine.bsd.uchicago.edu

I declare no competing interests.

1 Stefano A, Reyes LF, Faverio P, et al, on behalf of the GLIMP investigators. Global initiative for MRSA pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis* 2016; published online Sept 1. http://dx.doi.org/10.1016/S1473-3099(16)30267-5.
2 DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant *Staphylococcus aureus*. *Lancet* 2010; **375:** 1557–68.
3 Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* 2002; **359:** 753–59.
4 Geng W, Yang Y, Wu D, et al. Community-acquired, methicillin-resistant Staphylococcus aureus isolated from children with community-onset pneumonia in China. *Pediatr Pulmonol* 2010; **45:** 387–94.
5 Francis JS, Doherty MC, Lopatin U, et al. Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. *Clin Infect Dis* 2005; **40:** 100–07.
6 Gijón M, Bellusci M, Petraitiene B, et al. Factors associated with severity in invasive community-acquired *Staphylococcus aureus* infections in children: a prospective European multicentre study. *Clin Microbiol Infect* 2016; published online April 21. DOI: 10.1016/j.cmi.2016.04.004.
7 Olsen RJ, Kobayashi SD, Ayeras AA, et al. Lack of a major role of *Staphylococcus aureus* Panton-Valentine leukocidin in lower respiratory tract infection in nonhuman primates. *Am J Pathol* 2010; **176:** 1346–54.
8 Self WH, Wunderink RG, Williams DJ, et al. *Staphylococcus aureus* Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes. *Iin Infect Dis* 2016; **63:** 300–09.
9 Chickering HT, Park JH. *Staphylococcus aureus* pneumonia. *JAMA* 1919; **72:** 617–26.
10 Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and bacterial superinfection: illuminating the immunologic mechanisms of disease. *Infect Immun* 2015; **83:** 3764–70.
11 Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza Other Respir Viruses* 2016; **10:** 394–403.
12 Shah NS, Greenberg JA, McNulty MC, et al. Bacterial and viral co-infections complicating severe influenza: Incidence and impact among 507 U.S. patients, 2013–14. *J Clin Virol* 2016; **80:** 12–19.

Unravelling mucosal immunity to poliovirus


AP Cavallini James/BSIP/Science Photo Library

Published Online
September 13, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30371-1

See Articles page 1377

From an immunological perspective, the battle to eradicate polio is one of blood and guts. Induction of circulating poliovirus antibodies in blood is essential to block the spread of viruses to the CNS and thereby protect against paralytic disease. However, as eradication draws closer, the induction of immunity in the gut mucosa is becoming an ever-greater concern. Mucosal immunity is key to halting the spread of poliovirus from person to person, and thereby condemning the virus to extinction.

A major transition in the way that polio is immunised against is underway across the world. In April, 2016, use of the trivalent attenuated oral poliovirus vaccine (tOPV), which targets each of the three poliovirus serotypes, was replaced by a bivalent formulation targeting serotypes 1 and 3 (bivalent oral poliovirus vaccine; bOPV)—step one in the globally synchronised withdrawal of oral poliovirus vaccines that must occur to prevent polio caused by vaccine-derived poliovirus. To fill the gap in serotype 2 immunity, at least one dose of inactivated poliovirus vaccine (IPV) has been introduced into routine immunisation programmes in most countries that use oral poliovirus vaccines. Thus, in a matter of months, more than 100 countries have shifted from a routine schedule relying solely on tOPV to a mixed schedule of bOPV and IPV.

A major concern accompanying these shifts in vaccination policy is their implications for mucosal

immunity. Although oral poliovirus vaccine is known to induce a robust mucosal response (albeit one that wanes over time), IPV is only able to do so if individuals have been primed by previous exposure to live poliovirus (vaccine or wild-type).[1] In *The Lancet Infectious Diseases*, Peter F Wright and colleagues[2] report on a study seeking to clarify the impact of changes in routine vaccination on mucosal immunity to poliovirus. Infants from several countries in Latin America were immunised at 6, 10, and 14 weeks of age with bOPV, tOPV, or a mixed schedule of bOPV and IPV.[3] Mucosal immunity to serotype 2 poliovirus was assessed at 18 weeks by measuring poliovirus-specific antibodies in stool samples and shedding of poliovirus after administration of a challenge dose of monovalent serotype 2 (mOPV2) oral poliovirus vaccine. Although oral poliovirus vaccine challenge is the gold standard for measurement of mucosal poliovirus protection, attenuated vaccine viruses might fail to replicate for several reasons, including interference by concurrent enteroviruses,[4] so it is by no means perfect.

The assessment of antibodies in mucosal samples is fraught with complications, including cellular toxicity, dilution effects during sample collection, and the breakdown of immunoglobulin by proteolytic enzymes. Despite these constraints, Wright and colleagues successfully quantified the neutralisation titre of stool samples using serotype 2 polio pseudoviruses (comprising luciferase-encoding replicons surrounded by poliovirus capsid proteins). Neutralisation titre at the time of challenge was inversely correlated with the quantity of serotype 2 virus shedding 7 days later, supporting the use of this assay as a measure of mucosal protection. A similar association was not noted for poliovirus-specific IgA in stool, despite these antibodies being the probable mechanistic correlate of protection at the gut mucosa.

There are alternative approaches to measure mucosal immunity. A study[5] of children in India showed that the number of circulating poliovirus-specific antibody-secreting cells expressing the gut-homing integrin α4β7 could be a correlate of mucosal immunity. And in populations immunised with oral poliovirus vaccines, serum neutralising-antibody titres are a reasonable correlate of mucosal protection and are used by the Global Polio Eradication Initiative to monitor progress in high-risk areas.[6]

The study by Wright and colleagues also draws attention to one of the major obstacles currently facing the polio endgame: the deficits in serotype 2 mucosal immunity after a mixed schedule of bOPV and IPV. Of 87 infants who received this schedule, 53 (61%) shed virus 7 days after mOPV2 challenge, compared with just two (5%) of 38 infants who were vaccinated with tOPV. As the tOPV era becomes more and more distant, the cohort of infants who have never been exposed to live serotype-2 poliovirus and thus lack mucosal immunity will expand.

Serotype 2 polioviruses will hopefully be consigned to the history books soon. However, the resurfacing in August, 2016, of polio in Nigeria as a result of wild serotype 1 virus after more than 2 polio-free years provides a stark warning against complacency.[7] Comprehensive surveillance of children with acute flaccid paralysis and environmental samples is undoubtedly crucial to the success of the polio endgame. Even with robust surveillance, a pivotal question remains: how long has to pass without detection of polio before it can be concluded that the disease is gone for good?

*Edward P K Parker, *Nicholas C Grassly*
Department of Infectious Disease Epidemiology, St Mary's Campus, Imperial College London, London W2 1PG, UK
n.grassly@imperial.ac.uk

NCG is a member of the WHO Strategic Advisory Group of Experts on Immunisation polio working group. We declare no competing interests.

1 Herremans TM, Reimerink JH, Buisman AM, Kimman TG, Koopmans MP. Induction of mucosal immunity by inactivated poliovirus vaccine is dependent on previous mucosal contact with live virus. *J Immunol* 1999; **162:** 5011–18.
2 Wright PF, Connor RI, Wieland-Alter WF, et al. Vaccine induced mucosal immunity to poliovirus: analysis of cohorts in an open, randomised, controlled trial in Latin American infants. *Lancet Infectious Dis* 2016; published online Sept 13. http://dx.doi.org/10.1016/S1473-3099(16)30169-4.
3 Asturias EJ, Bandyopadhyay AS, Self S, et al. Humoral and intestinal immunity induced by new schedules of bivalent oral poliovirus vaccine and one or two doses of inactivated poliovirus vaccine in Latin American infants: an open-label randomised controlled trial. *Lancet* 2016; **388:** 158–69.
4 Parker EPK, Kampmann B, Kang G, Grassly NC. Influence of enteric infections on response to oral poliovirus vaccine: a systematic review and meta-analysis. *J Infect Dis* 2014; **210:** 853–64.
5 Dey A, Molodecky NA, Verma H, et al. Human circulating antibody-producing B cell as a predictive measure of mucosal immunity to poliovirus. *PLoS One* 2016; **11:** e0146010.
6 Craig KT, Verma H, Iliyasu Z, et al. Role of serial polio seroprevalence studies in guiding implementation of the polio eradication initiative in Kano, Nigeria: 2011–2014. *J Infect Dis* 2016; **213:** S124–30.
7 WHO. Government of Nigeria reports 2 wild polio cases, first since July 2014. http://www.who.int/mediacentre/news/releases/2016/nigeria-polio/en/ (accessed Aug 29, 2016).