3 Ladhani SN, Collins S, Djennad A, e. al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *Lancet Infect Dis* 2018; **18:** 441–51.

4 Kandasamy R, Voysey M, Collins S, et al. Persistent circulation of vaccine serotypes and serotype replacement after five years of UK infant immunisation with PCV13. *J Infect Dis* 2019; published online April 20. DOI:10.1093/infdis/jiz178.

5 Pilishvili T. Impact of PCV13 on invasive pneumococcal disease (IPD) burden and the serotype distribution in the US Advisory Committee on Immunization Practices: Oct 24, 2018. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-10/Pneumococcal-02-Pilishvili-508.pdf (accessed May 31, 2019).

6 WHO. Summary of WHO Position Paper on pneumococcal conjugate vaccines in infants and children under 5 years of age, February, 2019. https://www.who.int/immunization/policy/position_papers/who_pp_pcv_2019_summary.pdf?ua=1 (accessed May 31, 2019).

2017 ECIL 7 vaccine guidelines

We thank Laura Sticchi and colleagues[1] for their pertinent comments on the 2017 European Conference on Infections in Leukaemia (ECIL 7) vaccination guidelines for patients with haematological diseases, including haematopoietic stem-cell transplant (HSCT) recipients.[2,3] We answer their comments about antibody assessment below and address all other issues in the appendix.

See Online for appendix

Sticchi and colleagues first debate the use of antibodies for assessing vaccine immunity. The reasons our recommendations are mostly based on laboratory endpoints were explained in our Series papers:[2,3] for most vaccines, undertaking prospective trials that are powered enough to show the clinical benefit of vaccination in these populations is not possible. Until now, the largest prospective vaccine trial after HSCT included 251 patients.[4] Therefore, although prospective trials collect data on the occurrence of vaccine-preventable diseases, their primary objective is always a laboratory endpoint, except in cases of an outbreak when the infection incidence is high. We agree with Sticchi and colleagues that there are weaknesses in the use of antibodies for assessment of pre-existing immunity or vaccination efficacy, particularly for pathogens such as pertussis, which is why we did not suggest an individual assessment of anti-pertussis antibodies, although they have been assessed in prospective trials after HSCT.

Sticchi and colleagues also comment on the interest in opsonophagocytosis assays over ELISAs for assessing antipneumococcal and antipolyribosylribitol *Haemophilus influenzae* type b (Hib) antibody titres. We agree that opsonophagocytosis assays are rarely available in routine clinical practice; however, several prospective studies[4,5] have shown correlations between IgG ELISA antibody titres and opsonophagocytosis assay titres for all pneumococcal vaccine-induced antibodies assessed in allogeneic HSCT recipients. The largest study on the 13-valent pneumococcal conjugate vaccine (PCV13) in HSCT recipients, done in 54 paediatric and 162 adult patients, confirmed this strong correlation for all PCV13 antibodies, except for a small discrepancy for serotype 3 in children.[4] As for Hib anti-polyribosylribitol antibodies, we agree that their titres might sometimes not strictly correlate with their functions; however, first, after allogeneic HSCT, as we established in our 1987 publication[6] (before Hib vaccine was routine in children), an association exists between the onset of Hib disease and low anti-polyribosylribitol antibody titres assessed by ELISA,[6] irrespective of functional tests. Second, although anti-polyribosylribitol antibody titres decrease rapidly after vaccination in healthy children, nearly all those vaccinated maintain protective concentrations.[7] Finally, a large UK study using 2693 serum samples from individuals of all ages strongly suggested that anti-polyribosylribitol antibody titres at a concentration of 1 µg/mL or higher are protective of Hib disease.[8] The benefit of functional tests over ELISA is probably limited to the so-called grey zone of protection between 0·15 and 1 µg/mL in ELISA. In such a case in an HSCT recipient, without functional tests in routine practice, we would recommend a booster vaccination. In summary, we do not think functional tests are warranted in routine clinical practice (except for meningococcal immunity) because ELISAs can mostly provide useful individual patient-level information about the extent of protection, although no cutoff of protection has been established in this population.

Sticchi and colleagues question the assessment of antibodies against tetanus, diphtheria, and pertussis (Tdp) and Hib during long-term follow-up. After the initial regimen of three doses of Tdp vaccine, we recommend at least a booster programme according to the national recommendations for individuals of that age. However, the long-term (eg, 5-year) persistence of immunity after vaccination for diphtheria and tetanus after HSCT is good for tetanus but not for diphtheria, especially in patients who have extensive and chronic graft-versus-host disease.[9] Therefore, we hypothesise that high-risk patients (eg, those with extensive and chronic graft-versus-host disease, cord blood transplant recipients, or those receiving rituximab after transplant) might need boosters of vaccines earlier than is recommended in the healthy population.

Sticchi and colleagues also believe there was a contradiction between table 2 and the main text about assessment of pneumococcal antibodies,[1,2] which is not the case. In table 2, we gave the initial recommended programme for pneumococcal vaccination, and in the text we recommend the assessment of anti-pneumococcal antibodies from 24 months.

We agree with Sticchi and colleagues that many questions are still pending and encourage them to develop prospective vaccine studies in patients with haematological diseases.

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1 Sticchi L, Gabutti G, Castagnola E. Possible pitfalls of the 2017 ECIL guidelines. *Lancet Infect Dis* 2019; **19:** 575.
2 Cordonnier C, Einarsdottir S, Cesaro S, et al. Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis* 2019; **19:** e200–12.
3 Mikulska M, Cesaro S, de Lavallade H, et al. Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis* 2019; **19:** e188–99.
4 Cordonnier C, Ljungman P, Juergens C, et al. Immunogenicity, safety, and tolerability of 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine in recipients of allogeneic hematopoietic stem cell transplant aged ≥2: an open-label study. *Clin Infect Dis* 2015; **61:** 313–23.
5 Cordonnier C, Labopin M, Jansen KU, et al. Relationship between IgG titers and opsonocytophagocytic activity of anti-pneumococcal antibodies after immunization with the 7-valent conjugate vaccine in allogeneic stem cell transplant. *Bone Marrow Transplant* 2010; **45:** 1423–26.
6 Aucouturier P, Barra A, Intrator L, et al. Long lasting IgG subclass and antibacterial polysaccharide antibody deficiency after allogeneic bone marrow transplantation. *Blood* 1987; **70:** 779–85.
7 Collins S, Litt D, Almond R, et al. *Haemophilus influenzae* type b (Hib) seroprevalence and current epidemiology in England and Wales. *J Infect* 2018; **76:** 335–41.
8 Ladhani S, Ramsay M, Flood J, et al. *Haemophilus influenzae* serotype B (Hib) seroprevalence in England and Wales in 2009. *Euro Surveill* 2012; **17:** 20313.
9 Inaba H, Hartford CM, Pei D, et al. Longitudinal analysis of antibody response to immunization in paediatric survivors after allogeneic haematopoietic stem cell transplantation. *Br J Haematol* 2012; **156:** 109–17.

HIV crisis in Sindh, Pakistan: the tip of the iceberg

Pakistan has had a 45% overall increase in HIV cases from 2010 to 2017, with an annual incidence of 20 000.[1] According to Pakistan's National AIDS Control Programme (NACP), nearly 165 000 people are living with HIV nationwide, of whom only 24 331 (15%) are aware of their condition. In 2019, so far only 17 149 patients registered with NACP have received antiretroviral treatment (ART).[2] Poor awareness and illiteracy in rural areas of the country are likely to have adversely affected the AIDS control programme.

In April, 2019, an HIV outbreak was reported in the town of Ratodero in Larkana district, Sindh province, Pakistan. The outbreak was highlighted when 15 children with persistent fever were sent for HIV testing at a government-contracted facility and all were found to be infected. Blood reports were confirmed by another laboratory after referral from the Sindh HIV/AIDS Control Programme.[2] These astonishing results panicked the health administration because the chance of perinatal transmission was already ruled out in these children. HIV screening of residents of affected areas revealed more alarming results. 157 HIV-positive cases were identified after screening of more than 4100 people. Among individuals who tested positive, 30 were adults and 127 were children.[3] The Health Ministry and concerned officials did an inquiry to explore the cause of the outbreak and identified the reusing of contaminated disposable syringes as a possible factor. Syringes had been used multiple times by someone impersonating a doctor.[2]

The Pakistani Government, in collaboration with the UN, has taken some appreciable steps towards HIV prevention, such as ensuring the availability of treatment for patients and aiding specialised HIV investigations, but importantly prevention is also linked to awareness in the general population. National-level awareness campaigns, public speaking regarding risks factors, and frequent screening camps should be organised, particularly in remote areas, to aid early detection of index cases, thereby preventing further epidemics. Also, an urgent expansion of NACP is needed because ART is currently available to only 24 000 patients nationwide through 35 HIV treatment hubs. Only seven HIV treatment centres exist in Sindh province,[4] and all are in major cities, which probably leads to non-compliance since ease of availability of ART is likely to have a key role in adherence. In addition, law enforcement agencies should take strict legal action against individuals who impersonate health-care providers, since their malpractices are thought to be a primary reason behind various HIV epidemics in Pakistan in the past few years.

For more on **NACP** see https://www.nacp.gov.pk

HIV epidemics like this are not new to Pakistan—a similar outbreak occurred in January, 2019, in Punjab province.[5] This recurrence of rural epidemics within a short period of time should prompt initiatives to prevent such crises in the future.

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