blinded to DST) use of BPaLM and BPaL regimens could be especially high for rifampicin-resistant tuberculosis caused by lineage 1 strains, estimated to cause 28% of global tuberculosis, mainly in Africa and Asia.

Although there are no easy solutions for this complex issue, some things can be done now. The COVID-19 pandemic has boosted the global next-generation sequencing (NGS) infrastructure, which should be harnessed to predict resistance, guide rescue treatment in case of resistance or toxicity, and reduce knowledge gaps on resistance-associated mutations. Patients for whom treatment does not appear to be effective should have samples assessed by DST at reference centres. As we move forwards, rapid diagnostic tests, including targeted NGS, will be important. Data presented by Philip Supply and Viola Dreyer suggest that targeted NGS can detect resistance directly from smear-positive sputum[10] and maybe from stool samples.[11] These diagnostic approaches need validation and WHO endorsement to facilitate governmental investment and roll-out. We are fortunate to have more new drugs in the pipeline, but as a community we should demand that every new drug is developed alongside a companion diagnostic that will ensure the longevity of new regimens well into the future.

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The growing threat of wild poliovirus 1 and vaccine-derived cases in the COVID-19 era

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The detection of people with paralytic cases of wild poliovirus 1 (WPV1) in two African countries (ie, Malawi in February, 2022, and Mozambique in May, 2022) outside endemic areas of WPV1 transmission (ie, Pakistan and Afghanistan) will become a serious setback if low vaccination coverage and

decreased surveillance of acute flaccid paralysis are not addressed with alacrity.[1–3] Detection of vaccine-derived poliovirus (VDPV) outbreaks in new settings, including circulating vaccine-derived type 2 poliovirus (cVDPV2) in Ukraine in October, 2021, circulating vaccine-derived type 3 poliovirus (cVDPV3) in Israel in March, 2022, and cVDPV2 in the USA in July, 2022, and the environmental detection of VDPV in sewage systems in London, UK, in June, 2022, show the serious threat of polio re-emergence in settings that had previously interrupted polio transmission.[2,3] The COVID-19 pandemic has had a substantial role in diminishing the activities of national polio control programmes (eg, reducing their ability to conduct routine and supplemental immunisation activities and reducing acute flaccid paralysis surveillance).[4,5] The WPV1 type that was identified in two people in Malawi and Mozambique in 2022 has been epidemiologically linked to a viral strain that was previously identified in Pakistan in October, 2019, emphasising the ease of importation of wild poliovirus or VDPV unless high vaccination coverage (ie, >95%) is maintained along with investigation of all cases of acute flaccid paralysis, environmental monitoring, and outbreak response plans.[2,3]

The humoral response to oral poliovirus vaccine (OPV) prevents entry of wild poliovirus into the CNS and blocks replication on mucosal surfaces of the intestine.[4] However, by acquiring atypical genetic properties, strains of VDPV circulate in the environment, resulting in sustained person-to-person transmission. These strains, with reverted neurovirulence, can produce paralysis similarly to wild poliovirus in populations with low OPV coverage.[1,5,6] Inactivated poliovirus vaccine (IPV) offers protection against paralytic disease by inducing a strong humoral response but confers a weak mucosal response.

Global immunisation efforts and high-quality surveillance led to the last human case of wild poliovirus type 2 in 1999. By 2012, the last wild poliovirus type 3 infection was identified. Certification of eradication occurred in 2015 for wild poliovirus type 2 and 2019 for wild poliovirus type 3 infection.[1] However, endemic WPV1 transmission persists as a major concern in Pakistan and Afghanistan. Outside the endemic settings of WPV1 transmission, most cases of paralytic polio have been caused by circulating VDPV types in environments with low immunisation coverage.[3,4]

Before the COVID-19 pandemic, global efforts for the eradication of polio were suffering from the spread of outbreaks of cVDPV2 in many regions due to a fall below the 95% poliovirus vaccine coverage.[5] The eradication of wild poliovirus type 2 in 2015 was followed by a globally coordinated switch to bivalent OPV containing only type 1 and type 3 attenuated viruses.[1,4] This vaccination strategy was designed to reduce the risks of outbreaks of cVDPV2 and to boost immunity to the other serotypes. However, this globally synchronised transition occurred in early 2016 when IPV coverage was suboptimal in many settings, allowing the introduction of cVDPV2 in many countries.[5] Most regions with outbreaks of VDPV in the past 12 months have been in Africa (cVDPV2) until detection of cVDPV3 in Israel and detection of VDPV2 in the USA.[2,3] Although the Americas were certified free of polio in 1994, it is considered at high risk of resurgence given reductions in poliovirus vaccination activities and surveillance of acute flaccid paralysis. The Pan American Health Organization reported that, by 2020, only 80% of children received the third dose of poliovirus vaccine durine routine immunisation activities, which constituted a marked reduction compared with 2019.[2] In the Americas, vaccination coverage has decreased to below 95% in 33 of 42 countries.[2,3] Additionally, in endemic settings of WPV1 transmission, the vertical approach of polio control (ie, concentrating public health activities to only one disease) has led to programme fatigue and vaccine hesitancy, which has promoted programmatic deficits that, along with the ongoing civilian unrest, have left many clusters of children unvaccinated.[5]

The COVID-19 pandemic has further exacerbated the challenges in maintaining uniform vaccine coverage in every district or region by use of either OPVs or IPVs, which might eventually permit the rapid spread of cases of cVDPV2 in many settings and the threat of WPV1 reappearing in countries that have previously interrupted its circulation.[7] The realities of modern times, including competing public health priorities, geopolitical barriers, civil conflicts, and the risk of future pandemics, hinder governmental prioritisation of maintaining uniform vaccine coverage for global eradication of all circulating types of polioviruses.[4,5]

Implementing IPVs in all settings during routine and supplementary immunisation activities is central to reducing paralytic polio and fostering mucosal



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immunity among people with a previous history of OPV vaccination.[8] The ministries of health in all countries should achieve uniform vaccination coverage of more than 95% at national, subnational, and district levels. In settings with circulation of WPV1 or cVDPV, supplemental vaccination strategies, such as mass vaccination during national immunisation days, should be considered to maintain the highest levels of immunity. Countries that have implemented an initial dose of IPV need to introduce a second dose.[2,3] Additionally, decision makers should consider immunisation of travellers, people in war-torn areas, and migrants in transit from settings with endemic transmission or from locations with ongoing outbreaks of circulating VDPV.[9,10]

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