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COMMENTARY

Dangerous pathogens in the laboratory: from smallpox to today's SARS setbacks and tomorrow's polio-free world

Less than a year after an unprecedented international public-health effort interrupted human-to-human transmission of the coronavirus that causes severe acute respiratory syndrome (SARS-CoV), some human beings are again infected. SARS-CoV does not seem to have re-entered the human population from the exotic wild-animal markets of China that have preoccupied public-health officials worldwide, nor from some other source in nature not yet understood. Rather, the latest outbreak seems to be from a laboratory source.[1]

This scenario is reminiscent of the often forgotten footnote to the smallpox eradication effort when the last human infections did not occur in Somalia, the last country with naturally occurring smallpox, but a year later in Birmingham, in the UK, originating from a laboratory with inadequate biosafety facilities.[2] Auspiciously, the new SARS cases are occurring as WHO's Biosafety Advisory Group prepares to examine the long-term containment of poliovirus stocks, the risks of which will rapidly increase after interruption of transmission and the ending of immunisation with oral poliovirus vaccine.[3]

The recent outbreak of nine cases of SARS in China, with one death, underlines again the challenges of maintaining appropriate biosafety conditions in laboratories working with dangerous pathogens. In this outbreak, two researchers at the Institute for Viral Disease Control and Prevention in Beijing developed SARS in late March and mid-April.[4] All subsequent second-generation and third-generation cases have now been linked to close contact with one of these researchers. Investigation of the source of the outbreak, jointly by the Chinese Ministry of Health and WHO, continues to focus on this virology institute.[1]

If the laboratory source is confirmed in China, this will be the third known incident of laboratory-acquired SARS-CoV infection, the first having occurred at the National University of Singapore where a postgraduate developed an illness consistent with SARS in late August, 2003.[5] During the investigation that followed, it was concluded that the student most probably acquired the infection in the BSL-3 laboratory in which he was studying the West Nile virus 3·5 days before the onset of his illness, which is consistent with the expected incubation period of SARS. (Biosafety conditions are described as biosafety levels in four categories [BSL 1–4], with BSL-3 and BSL-4 recommended for work with pathogens that cause serious human and animal disease). It seems that transmission occurred as a result of inappropriate laboratory procedures that led to cross-contamination of the West Nile virus specimen with SARS-CoV. No other workers in the laboratory, and none of the medical staff who cared for the student while he was ill, became secondarily infected, nor did household and other contacts.

The second reported incident similarly resulted in an isolated case of SARS in early December, 2003. It occurred at the Institute of Preventive Medicine, National Defence University, Taipei, in a laboratory scientist who had been working intensely in a BSL-4 laboratory, over a long period and for long hours each day.[6] It seems that transmission occurred after exposure to SARS-CoV from contact with droplets when cleaning the spill of a SARS-containing specimen in the laboratory's transport chamber.

Accidental transmission of a dangerous pathogen from a laboratory can occur when a susceptible and unprotected laboratory worker is exposed to the agent during laboratory procedures. These conditions were met in the smallpox laboratory in Birmingham in 1979, and in at least two of the laboratories associated with the recent cases of SARS during 2003. If the resulting human infection causes viral shedding, with exposure to susceptible workers in the laboratory, health-care system, or community, an outbreak can result. In the outbreak in Brimingham after the smallpox laboratory accident, infection spread from the initial case to a close family member and one other. In the current outbreak of SARS, chains of transmission seem to have moved from the laboratory, to a close family member, and to a hospital, from where a nurse who treated the laboratory worker then transmitted infection to five others.

Proven measures to minimise the risk of reintroducing dangerous pathogens include: limiting the number of sites where they are stored and studied to those that are absolutely necessary; protection of laboratory workers with available vaccines, protective clothing, and safe equipment; closely monitoring illnesses in laboratory workers; and adhering to standard operating procedures. Hundreds of years of combined experience in high and maximum containment laboratories have proven these biosafety measures effective if rigorously and faithfully followed—with strict national procedures to verify that appropriate conditions and procedures are maintained.

After certification of smallpox eradication, known stocks of variola virus were destroyed or transferred to one of two WHO reference laboratories where biosafety is periodically verified by the WHO Biosafety Advisory Group. During the SARS outbreak last year, many specimens were obtained from human cases of SARS

and sent to many different national and international laboratories for various studies. In April, 2003, WHO provided guidelines for handling, packing, and shipping SARS specimens, and listed laboratory practices that could safely be done under BSL-2 and those that required BSL-3.[7] These guidelines were reviewed and updated during later WHO consultations, and laboratory research activities continue at many of these sites.[8] Unfortunately, adherence to these guidelines has now failed at two, and possibly three, different laboratories, reaffirming the importance of strong national, and possibly international, monitoring of their implementation. The predictable emergence of new dangerous pathogens in the future further highlights the need for such action.

If activities to eradicate poliomyelitis remain on target, interruption of human-to-human transmission will occur sometime during the next 18 months, and the wild poliovirus will be moved from the list of endemic infections to that of dangerous pathogens. That poliovirus reintroduction could occur was seen in 1992 when a reference strain of wild-poliovirus type I that is used in the production of inactivated poliovirus vaccine was isolated from a young child being investigated for diarrhoea.[9] The subsequent epidemiological investigation found that the child's father was employed at a production site for inactivated poliovirus vaccine where an accident had occurred. Fortunately the child was fully immunised against poliovirus. But the child served as a healthy carrier of poliovirus to the community, although sanitation was adequate and poliovirus vaccination coverage was high enough to prevent an outbreak. A similar poliovirus reintroduction from a laboratory or production facility for poliovirus vaccine to one of the many countries that have indicated their intention to stop poliovirus immunisation after certification of global eradication could result in future outbreaks of poliomyelitis.[10]

Recognising the risks that would be associated with a poliovirus reintroduction, WHO and its technical partners in poliomyelitis eradication began the process of establishing a global action-plan for the long-term laboratory containment of wild polioviruses in the mid-1990s.[11] By 1999, international consensus had been established and the process of surveying and inventorying laboratories for wild poliovirus and infectious or potentially infectious materials began in the three WHO regions that had interrupted indigenous transmission of wild poliovirus. Through the comprehensive surveys of national laboratories that are underway or completed in 152 countries in five continents, over 160 000 facilities have been inventoried to date. About 500 facilities have reported wild-type poliovirus or potential infectious materials. At the same time, technical and engineering solutions have allowed the continued production of inactivated poliovirus vaccine from wild poliovirus under enhanced BSL-3 conditions to ensure that such a vaccine is available to the countries that choose to continue routine immunisation against the poliovirus after eradication has been certified globally and the routine use of oral poliovirus vaccine stopped.[12]

The current WHO plan for the period after the global interruption of wild-poliovirus transmission specifies BSL-3 conditions for wild-poliovirus infectious materials and BSL-2 for potentially infectious materials in non-virology laboratories, on the basis of a now outdated assumption of continued universal immunisation.[11] In September, 2003, an expert group recommended that because circulating vaccine-derived polioviruses would, like wild poliovirus, compromise the goal of poliomyelitis eradication, the use of oral poliovirus vaccine for routine immunisation should eventually stop.[13,14] This decision, combined with the recognition that many countries plan to forego future routine immunisation with inactivated poliovirus vaccine, has led to the understanding that Sabin poliovirus strains will also need to be stored and handled under appropriate biosafety conditions. A biosafety strategy for minimising the risk of a laboratory accident with the Sabin poliovirus is under development. In addition, consensus is being sought on the mechanisms and procedures for ensuring that the necessary stockpiles of oral poliovirus vaccine are available should poliovirus be reintroduced into human populations because of a laboratory accident.

Although an increasing number of pathogens are referred to as dangerous, in reality different pathogens present different laboratory risks. SARS-CoV seems to represent a high laboratory risk. Unlike SARS-CoV, poliovirus is not efficiently transmitted by droplets from person to person, and a vaccine is available that fully protects laboratory workers from disease and reduces the risk of infection, thereby providing additional assurances against substantial consequences should a laboratory accident occur once routine immunisation with oral poliovirus vaccine has stopped. It is also reassuring that no further accidents have occurred with the smallpox virus stored in two reference laboratories for over 20 years. Nevertheless, the recent laboratory accidents with SARS-CoV are a stark reminder that the security of public-health achievements requires greater investment to ensure that global biosafety standards for dangerous pathogens in laboratories are universally adopted, strictly adhered to, closely monitored, and rigorously enforced.

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How to prevent cannabis-induced psychological distress . . . in politicians

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Cannabis can cause anxiety, agitation, and anger among politicians. The consequences of this cannabis-induced psychological distress syndrome (CIPDS) include overreaction with respect to legislation and politics and a lack of distinction between use and misuse of cannabis. In times of a war against drugs, this distinction might even be regarded as unpatriotic,[1] as irresoluteness in the face of the enemy. One trend associated with CIPDS involves taking away the driving licence of people who drive and are discovered to have inactive tetrahydrocannabinol metabolites in their urine.[2] In a more severe state of paranoia even medicinal use can be perceived as a threat to society, since it might "destabilize the societal norm that drug use is dangerous",[3] ignoring the fact that many prescription and over-the-counter drugs are potentially harmful. Exaggerated laws on cannabis made by anxious individuals could be regarded as a modern version of the generational conflict.[4]

Rationality and factuality are needed to calm down politicians affected by CIPDS. That cannabis might cause infertility, cancer, cognitive decline, dependency, traffic accidents, and heart attacks, and that it can lead to the use of more dangerous drugs, are all arguments that have been used to justify the war on cannabis. Drugs can be harmful, whether they are legal or illegal, but claims about the dangers of cannabis are often overstated.[5,6]

One main justification for today's war on cannabis is its possible detrimental effect on the mental health and social wellbeing of adolescents. In this week's *Lancet*, John Macleod and colleagues show that the causal relation is less certain than often claimed, and point out several common misunderstandings about the difficulties encountered when studying drug use, such as the limits of confounder adjustment. The results of one often-cited Swedish study,[7] for example, indicate a crude odds ratio of 6·7 for schizophrenia risk at age 26 years in individuals who used cannabis more than 50 times before age 18 years. This finding suggests cannabis is an important contributor to schizophrenia. After adjustment for several possible confounders, however, the risk decreased to 3·1, a strong indication of residual confounding—ie, the presence of factors that would further reduce the risk if included in the statistical model but that could not be included because of a lack of data.

Another review[8] details the findings of an investigation into the association between cannabis and psychosis on the basis of five longitudinal studies. The authors conceded that only one of these studies was able to record whether prodromal manifestations of schizophrenia preceded cannabis use. The results of the study[9] indicated that "cannabis users at age 18 years had elevated scores on the schizophrenic symptom scale only if they had reported psychotic symptoms at 11 years",[8] and that people who used cannabis at age 15 years had a higher risk for adult schizophreniform disorder at age 26 years even if psychotic symptoms at age 11 years were controlled for.[9] The researchers concluded that cannabis was a causal factor for psychosis in "vulnerable youths".[8]

There is some reason to believe that cannabis contributes to psychosocial problems in adolescents and young adults, and no responsible adult would want young people to take drugs. There is no question that this issue is an important candidate for education and prevention, but there is a fierce debate on the place repressive measures should have in this context. There is little reason to believe that criminalisation has had a strong effect on the extent of cannabis use by young people.[10] Moreover, prohibition itself seems to increase the harmfulness of drug use and cause social harm.

By stopping all cannabis users from being treated as criminals, I believe this year's change by the British Government of its cannabis law (a declassification from class B to C) is a sensible attempt to balance the possible harms caused by cannabis and its prohibition. The concern expressed by Peter Maguire of the British Medical Association and others,[11] that "the public might think that reclassification equals safe", is based on the wrong assumption that cannabis became illegal because its use is unsafe and dangerous. Many unsafe activities are legal, including skiing downhill, having sex, drinking beer, eating hamburgers, and taking aspirin. Cannabis did not become illegal because it was shown to be dangerous but, more likely, because Harry Anslinger, Commissioner of the US Bureau of Narcotics 1930–62, and his colleagues needed a new target and battlefield after the end of alcohol prohibition in 1933. Reputed dangers, presented in his statements before the US Senate in 1937,[12] were used as a shocking means of manipulation—eg, "A man under the influence of marijuana actually decapitated his best friend; and then, coming out of the effects of the drug, was as horrified as anyone over what he had done." The representative of the American Medical Association strongly opposed the Marijuana Tax Act of 1937: "To say . . . that the use of the drug should be prevented by a prohibitive tax, loses sight of the fact that future investigation may show that there are substantial medical uses for cannabis."[13]

We live in a time in which the unrealistic and unproductive paradigm of complete abstinence from drugs is slowly dissipating. Proponents of a drug-free society find this fact hard to accept, and responsible politicians and doctors can find achieving an appropriate position in the debate difficult. However, we must learn to deal with drugs and their possible dangers without fear.

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