

# Human Infection Challenge Experiments: *Then and Now*

**ABSTRACT** In the midst of the Covid-19 pandemic, ethicists, researchers, and journalists have recommended studies that deliberately infect healthy volunteers with the coronavirus as a scientific means of expediting vaccine development. In this essay, we trace the history of infection challenge experiments and reflect on the Nuremberg Code of 1947, issued in response to brutal human experiments conducted by Nazi investigators in concentration camps. We argue that the Code continues to offer valuable guidance for assessing the ethics of this controversial form of research, with respect particularly to the acceptable limits to research risks and the social value of research necessary to justify exposing human participants to these risks. **KEYWORDS** human subjects research, human research ethics, infection challenge experiments, research risks, social value, independent review, Nuremberg Code.

In 1900, Major Walter Reed of the U.S. Army led experiments in Cuba in which research volunteers were deliberately exposed to mosquito bites in order to test the hypothesis that the mosquito is the vector for transmission of yellow fever.<sup>1</sup> A physician-investigator who volunteered to be a research subject died after contracting yellow fever. And Clara Maass, a 25-year-old army nurse, died after volunteering for a subsequent human challenge experiment conducted by The Yellow Fever Board;<sup>2</sup> she may be the only person honored with a postage stamp by both the United States and Cuba. In view of many deaths in the United States caused by epidemics of this viral disease, this scientific contribution to the cause of understanding its transmission, which informed how to prevent it, was widely regarded as heroic. Forty-six years later, Telford Taylor, in his opening statement for the prosecution

of Nazi physicians and bureaucrats in the Nuremberg doctors' trial detailed brutal Nazi medical experiments conducted in concentration camps.<sup>3</sup> These included deliberate exposure of Dachau inmates to malaria, which caused numerous deaths from both the infection and toxic doses of potential treatments, and exposure of inmates at Buchenwald and Nazweiler to typhus, aimed at testing vaccines. Taylor reported that "[a] dozen or more of the defendants were involved in these experiments, which were characterized by the most cynical disregard of human life."<sup>4</sup>

The Nuremberg Code specifying ethical requirements for human experimentation was written by the judges.<sup>5</sup> It is a landmark document, consisting of 10 provisions that have laid the foundation for much subsequent ethical guidance regarding protection of subjects of biomedical research.<sup>6</sup> One of the provisions of the Code, which we discuss below, contains a possible exception to its guidance that harks back to Walter Reed's yellow fever research: "No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects."<sup>7</sup>

Also lauded as heroic research was the participation of prisoners in malaria infection challenge experiments conducted at Stateville Penitentiary in Illinois from 1944-1946, experiments in which inmates were exposed to mosquito bites for the purpose of evaluating treatments for the disease.<sup>8</sup> *Life* magazine ran a photo-spread article on this research, which declared that "enemies of society are now helping science fight another enemy of society."<sup>9</sup> This article was used by Robert Servatius,

counsel for the defense of Nazi physician Karl Brandt at Nuremberg, to suggest that U.S. scientists had been doing the same thing as the Nazis under trial. While the Stateville experiments were ethically problematic, unlike with the Nazi experiments, death was not an anticipated or planned endpoint (although one prisoner did die), and prisoner volunteers were recruited who gave their consent.

The prospect of investigators deliberately infecting human subjects for the sake of developing scientific knowledge might seem morally objectionable. However, in the past 40 years, numerous experiments of this sort, involving malaria, cholera, influenza, dengue, and other diseases, have been conducted safely under controlled conditions with careful attention to minimizing risks to subjects and with the approval of research ethics committees. Valuable knowledge about infectious diseases has been gleaned from such research, which has also provided important contributions to the development of licensed vaccines.

Until very recently, contemporary human infection challenge studies have received scant public attention, and ethical reflection on such research has occupied a small niche within the bioethics and medical literatures. In the wake of the coronavirus pandemic, some ethicists, epidemiologists, vaccine researchers, and journalists strongly advocated the use of coronavirus infection challenge experiments as a tool for expediting vaccine development.<sup>10</sup>

Conor Friedersdorf, a staff writer for the *Atlantic*, described an organization, The Covid Challenge, that has signed up a large number of volunteers interested in participating in a coronavirus infection challenge study.<sup>11</sup> Friedersdorf described this type of research as “an ethical *imperative*.” On April 20, 2020, 35 members of the U.S. Congress wrote a letter to the secretary of the Department of Health and Human Services and the commissioner of the Food and Drug Administration in which they voiced support for coronavirus infection challenge trials.

Three provisions of The Nuremberg Code provide guidance that is particularly pertinent to the question whether a coronavirus infection challenge study should be undertaken at this time. The first is the provision quoted above, which precludes studies “where there is an *a priori* reason to believe that death or disabling

injury will occur.” Despite the vast and growing literature on the ethics of human research, there remains no consensus on this vital question: what are the limits of risk to healthy volunteers that can be justified in a study with significant scientific and social value? We believe that this provision of the Code offers a reasonable rule of thumb. Suppose that a proposed program of one or more coronavirus infection challenge studies were to recruit 100 young, healthy participants, all of whom would be exposed to a strain of the virus. It has been estimated that the risk of death and hospitalization to healthy volunteers aged 20 to 29 in a carefully designed and monitored study would be respectively 0.03 and 1.1%.<sup>12</sup> Thus, it would be highly unlikely that one or more participants in such a study would die or suffer disease requiring placement on a ventilator and resulting in long-lasting disability. Hence, this study would be consistent with the risk limit guidance of the Code. In view of the urgency of the coronavirus pandemic, perhaps some might think that even a 1% risk of death could be justified with respect to young, healthy volunteers giving genuine informed consent—the requirement specified by the first provision of the Code.

Detailed ethical guidance for injection challenge studies was initially published in 2001.<sup>13</sup> That article suggested that these studies should be conducted only for diseases that either are self-limiting, without serious adverse events, such as the common cold, or treatable in a way that can eradicate the infection a short time after experimental exposure, such as cholera and malaria. Subsequent ethical guidance has generally followed that position, which would preclude infection with the coronavirus causing the current pandemic. However, we see no reason to insist on the availability of effective treatment if the risks to participants are sufficiently low.

It is ethically important to recognize that an acceptable level of risk to participants and obtaining informed consent are not jointly sufficient to justify the conduct of an infection challenge experiment. Two, closely related, provisions of the Nuremberg Code address another ethically essential consideration: “[t]he degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment,” and “[t]he experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and

not random and unnecessary in nature.” Together, the guidance of these two provisions has become known as the *social value requirement*.

The advocacy argument for a coronavirus infection challenge trial during the early months of the pandemic took the following form.<sup>14</sup> A challenge study *could* speed vaccine development (a goal of obvious humanitarian importance); the risks to young, healthy participants giving informed consent would not be excessive; therefore, such a challenge study *should* be conducted. But this is much too quick. Critical to deciding whether to undertake such a challenge study at that time, or in the future, is the question whether it would offer sufficient potential social value to justify the risks to participants. In fact, by the end of 2020, the Operation Warp Speed initiative in the United States led to the development of two innovative mRNA Covid-19 vaccines, which were shown to be highly effective in large-scale field trials—less than a year after the emergence of the pandemic. It is difficult to see how conducting a challenge study could have expedited vaccine development. Whether human infection challenge research can play a useful and ethically justifiable role in the future is open to question. Nonetheless, in February 2021, the United Kingdom’s government approved an initial challenge trial to determine the viral dose necessary to produce coronavirus infection in human volunteers.<sup>15</sup>

Reflection on the history of infection challenge experiments illustrates how a method of scientific investigation with considerable potential for developing knowledge of great humanitarian importance can be abused in unethical applications or conducted legitimately in accordance with high ethical standards. These standards include substantial potential social value, risks to participants that are not excessive and justified in light of that social value, and scrupulous procedures for obtaining informed consent. ♦

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