Review

Experimental infections in humans—historical and ethical reflections

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Abstract

Vaccine efficacy and prophylactic treatment of infections are tested best when the vaccinated or treated individual is challenged through deliberate infection with the respective pathogen. However, this trial design calls for particular ethical caution. Awareness of the history of challenge trials is indispensable, including trials that were problematic or even connected to abuse. We briefly introduce historical aspects of experimental infections in humans and the ethical debate around them and give estimates of the numbers of volunteers participating in human experimental infection models. Challenge models can offer a great chance and benefit for the development of medical interventions to fight infectious diseases, but only when they are appropriately controlled and regulated.

keywords Experimental infection, vaccines, challenge trials, ethics, medical history

Introduction

Many laypersons assume that intentional infection research on humans is either illegal or no longer being performed, or only performed on a small number of persons in few locations. But experimental infections in humans (challenge studies) have a long tradition and remain commonplace [1].

Especially in the 18th and 19th centuries, knowledge about the origin, course and transmission of infectious diseases were gained through experiments and auto-experiments in humans. The Scottish doctor John Hunter infected test subjects, and possibly himself, with pus from individuals with venereal disease in order to study syphilitic fever. His advice to Edward Jenner became famous: 'Try the experiment' [2]. René Nicolas Dufiche Baron Desgenette and Alexandre-François Ollivier, both surgeons in Napoleon’s army, inoculated themselves with germs of bubonic plague and 'pourriture d’hôpital' (the rot of the hospital), respectively, in order to better understand the origin of pest and gangrene, two infections debilitating soldiers in their contingents [3,4].

Vector-borne infections and viral diseases were subject to similar experiments. In 1900, Walter Reed, an American army surgeon, exposed test persons to mosquitoes infected with yellow fever virus in order to verify its mode of transmission. Tragically, three test persons and a physician of his team died in the course of the trial [5,6]. Also dating back to the time of World War I, influenza virus was studied by experimental infections: during the epidemic, healthy subjects were intentionally exposed to patients in order to investigate the transmission of the virus [7]. After World War II, the so-called Common Cold Unit was built in Salisbury (UK) and presumably over 19 000 volunteers in more than 1000 studies were experimentally infected with viruses [8,9].

A recent example for the aetiological identification of an infectious agent via an experimental infection is Helicobacter pylori. Although spiral bacteria have been observed in the human stomach since the end of the 19th century [10], it was not until 100 years later that the microaerophilic bacterium Helicobacter was identified as a causative factor of gastric and duodenal ulcer [11]. The groundbreaking experiment was carried out by Barry Marshall, an Australian investigator, who drank a beaker with cultured bacteria and then developed acute gastritis. Thus, he could demonstrate that Koch’s postulates are fulfilled and that the bacteria are not only an accompanying phenomenon [12].

Regarding the evaluation of the safety and efficacy of prophylactic treatment or vaccines, Edward Jenner was one of the first to report an experimental infection of humans. In 1796, he inoculated his neighbour, James Phipps, with the yield of the pustule of a cowpox patient.
Six weeks later, he variolated him. In this way, Jenner tested the effect of the vaccine with an inoculation of human smallpox [13]. Similar experiments were performed in the 19th century, for example to find a vaccine against plague, sadly with negative results [14]. Even in the first half of the 20th century, two German physicians tried to prove the efficacy of a tetanus vaccine with an auto-challenge experiment: after vaccination they injected themselves with tetanus toxin and survived [15].

From today’s view, these early efficacy experiments are of little significance because infections were non-standardised, control groups did not exist and case numbers were small. Thus, the evidence gain is small since other factors may have had an impact on the results. It was not until the 1950s that standardised experimental infections in humans were established which applied modern trial designs with larger samples, random allocation and control groups [16]. Guidelines were formulated, and a central registry for all microbial challenges in human volunteers was postulated [17].

**Experimental infections in humans and early regulations**

Although intentional pathogen inoculations of humans have considerably increased our knowledge of aetiology, course, treatment and prevention of communicable diseases, one should not forget that such experiments raise particular ethical concerns. Essentially, the inoculation of a pathogen is an act of harming an individual and contradicts the principle of non-maleficence. Such experiments may risk serious damage and get out of control. Experimental infections can become inhumane and even criminal, especially when disease states are provoked.

Hence, it is not surprising that experimental infections in humans are tightly linked to the history of scandals in medical research. Frequently, ethically questionable, unjustifiable, or criminal experiments were followed by efforts to regulate the experiments with respect to humane conduct.

German history of medicine is a rich example for this phenomenon. At the end of the 19th century, German scientists were influential in medical research. A popular subject of scientific interest was syphilis, and women, mostly prostitutes, served as test persons [18]. For instance, the renowned bacteriologist Albert Neisser applied the serum of syphilis patients to prostitutes and orphans in order to test a vaccine against syphilis—without their consent and without even informing them. Some of them contracted syphilis and, although a parliamentarian commission had approved the experiment, a strong public debate ensued [19]. It centred on the question whether test persons have to be informed and consent to the experiment. As a consequence, in 1900, the otherwise rather martial Prussian government authored a directive on the conduct of medical experiments in humans. This was the first document to recognise the need for protection of vulnerable groups and informed consent [20].

In 1931, ethical regulations for medical experiments in humans were advancing a step further. The death of 77 children caused by a contaminated vaccine against tuberculosis [21] led to the development of guidelines on human experimentation [22]. These may be considered the birth of modern regulation of medical procedures [23].

**Experimental infections in humans in Nazi Germany**

However, there was no time for this guideline to unfold its impact. Two years later, the party of Adolf Hitler came to power and German physicians started experiments in humans. Most studies were meticulously documented. A minimum of 15,754 victims, of whom 4,123 died, were identified in the study records [25]. For experimental infections, various germs and infectious materials were used as follows: streptococci, pus of teeth, malaria parasites, Salmonella typhi and paratyphi, yellow fever virus, material of gas gangrene, Rickettsia, Mycobacteria, Chlamydia, Vibrio cholerae, and influenza viruses were among the pathogens used to infect prisoners of concentration camps [24].

Interestingly, this was not unknown to the international research community. In 1943, vaccination experiments at German concentration camps were mentioned as revealing for vaccine development in a publication of The Lancet [26]. In a controlled study with 1000 prisoners in three groups, Rickettsia prowazekii preparations were inoculated intramuscularly, subcutaneously, or intravenously. The vaccine was not efficacious and nearly all test persons died or suffered severe health damage [27].

Vector-borne infections were also studied. Claus Schilling, a student of Robert Koch and later professor and director of the Robert Koch Institute in Berlin, tested drugs and vaccine candidates in inmates of the Dachau concentration camp. He infected more than 1000 prisoners with Plasmodium falciparum; more than 300 prisoners died [28]. His successor, Gerhard Rose, investigated infective agents in inmates, mentally ill persons and prisoners of war. Many did not survive the experiments [27]. Schilling was hanged in 1946 [29], whereas Rose was rehabilitated after a short prison term and continued to practice medicine. In July 1977, he was awarded a prize for ‘outstanding services to matters of military hygiene’ in Germany [30].

In response to the crimes committed by Germans in the name of medical science, the so-called Nuremberg code...
Experimental infections in humans after World War II

In the United States, this code was considered ‘a good code for barbarians’, but ‘superfluous for the normal medical researcher’ [32]. However, the years after World War II saw an increasing number of infection experiments carried out by North American research institutions [33] with questionable consent procedures. For example, between 1946 and 1948, John C. Cutler, a physician of the United States Public Health Service, deliberately infected more than 1500 Guatemalan inmates, soldiers, and mentally handicapped men and women with syphilis and other sexually transmitted pathogens to investigate new drugs. Amongst others, liquid solutions with syphilis bacteria were trickled in open wounds, face or male and female genitalia [34].

In 1966, 22 examples of ethically doubtful studies were listed in a groundbreaking paper [35]. The names of several places where they occurred became synonymous with unethical research, such as ‘Willowbrook’, a state school for mentally disabled children in Staten Island, United States. There, children were injected with hepatitis virus to test passive vaccination. These studies lasted for more than 15 years. An important discovery was the discrimination between Hepatitis A and B virus. However, the project attracted criticism because parents were not truthfully informed about the risks of the investigations, and children were involved with the prospect of harm rather than benefit [35]. Willowbrook became synonymous with a controversial conflictive discussion of ethical considerations. Pro-arguments were as follows: (i) The experiments were potentially beneficial for participants because the ‘passive-active immunity’ hypothesis could have been true; (ii) the experiments conferred the additional benefits of closer observation and extra medical care in the context of the experiment to participants; (iii) the risk of infection was not substantially higher than outside the experiment because of the high likelihood to get infected with hepatitis viruses while being a resident in Willowbrook; (iv) the general risk was even reduced because the strain of hepatitis virus used in the experiment was the one prevalent in Willowbrook, which allegedly led to a particularly mild infection [36].

Whether these assumptions were referring to facts in Willowbrook cannot be evaluated at this point. What is of interest is the general ethical content of these arguments. Arguments 1 and 2 refer to a potential benefit from participating in a challenge experiment, which may consider being infected under particularly well-controlled conditions. This is connected to arguments 3 and 4, referring to the risk assessment. Argument 3 especially is relevant to challenge trials today as it is based on the assumption that risks for trial participants have to be assessed against the background of their living conditions. Similar arguments were discussed in respect to Walter Reed’s famous Yellow Fever experiments [5,37,38].

It was not until public debates about another syphilis study, the so-called Tuskegee experiment [39], gained momentum that a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in the United States in 1974 [40].

Today’s ethical and regulatory base of experimental infections in humans

Today, all experimental infections in humans are subject to global and strict legal regulation [41]. The central document is the declaration of Helsinki, which is updated regularly to reflect the ongoing discussion [42]. As for all clinical studies involving the participation of human subjects, the international quality standard for the ethical and scientific quality of designing, conducting, recording and reporting experimental infections in humans is the Good Clinical Practice (GCP) guideline provided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) [43].

From an ethical point of view, experimental infections are similar to dose-finding studies in Phase I trials with healthy human volunteers, where the maximally tolerated dose of a compound is assessed [17,44–46]. Just as escalating doses will potentially cause side effects, deliberate pathogen inoculation will potentially harm trial participants.

The ethical assessment of experiments resulting in infection can be framed by the following criteria:

1. Is the scientific rationale for using a particular pathogen challenge model acceptable?
2. Are the risks of the particular challenge model acceptable?
3. Are the discomforts resulting from infection after pathogen challenge acceptable?
4. Does the challenge experiment enroll subjects from a vulnerable population? [46].

The argument that the risk inside a trial is hardly higher than outside it might be particularly relevant for research ethics in low- and middle-income countries. The
question whether such a justification can be accepted leads to difficult subsequent questions:

- Is the risk of infection outside the trial known precisely enough for such a justification?
- Are there ways to reduce this risk, or change the context for the trial participants—for example will behavioural or ambiential changes to improve this risk be disregarded in order to carry on with the challenge experiments?
- Can providing medical care in such a context be regarded as an undue inducement to participate in a risky clinical trial for the benefit of others? To which degree would it be possible to provide the necessary care outside a particular trial?
- A higher risk of being exposed to an infectious agent may also be the result of disadvantaged living conditions. Using this degree of risk as a justification to select trial participants may add further injustice to this situation, since people who are already in a disadvantaged position may also bear a disproportionate burden resulting from the participation in clinical research.

For these reasons, justifications for challenge experiments better be based on informed consent of participants and an acceptable level of risk. Using potential benefits for trial participants or their background risks as additional arguments for their inclusion is problematic at best. Such additional arguments should be evaluated with caution, and on a case-to-case basis.

According to Grady and Miller [46], human challenge infections can be grouped in three categories:

1. **Legitimate challenge models**, comprising infection with a rapid onset of tolerable symptoms and infections that are self-limiting or that can be adequately treated and eradicated with certainty. Examples: hookworms, cholera, *Plasmodium falciparum*.

2. **Potential challenge models**, comprising infections that are characterised by less-than-full confidence in eradication, the possibility of chronic disease, and/or an increased but small risk of serious morbidity or mortality. Examples: Lyme disease, *Helicobacter pylori*.

3. **Unacceptable challenge models**: infections for which treatment is non-existent or ineffective, symptoms are intolerable, and/or serious morbidity or mortality is likely to result. Examples: Ebola virus, tetanus, rabies.

Challenge infections with the spectrum of pathogens limited to category 1 are ethically justifiable and are uncontroversial in the pertinent literature. Category 2, which seems to be acceptable to Grady and Miller, will certainly raise concerns among ethicists and members of ethics committees. However, international ethical guidance documents do not define absolute limits for risks of harm. Instead, the Declaration of Helsinki ties the acceptable risk of a particular trial to its potential benefit for society [42,46]. While this does not *prima facie* provide a justification for challenge experiments with pathogens from category 2, such experiments are not ruled out but require individual evaluation. Needless to say the potential benefit for society alone does not make a trial justifiable as this holds true only within the ensemble of trial conditions.

Besides objections for ethical reasons and thus the small number of pathogens suitable for challenge studies, intrinsic limitations of the challenge model have to be considered: The challenge population might differ from the population at risk for natural disease; most volunteer models measure only short-term protection; efficacy estimates may lack precision owing to small sample size; and mechanisms of experimental infection may differ from natural infection, for example the size of the inoculum is often larger than what is naturally encountered [47].

### Numbers of volunteers in human challenge trials

The literature search for experimental infections in humans is exigent because reporting of challenge studies is poorly standardised and specific terms do not exist, a problem that was the object of another investigation [48] already. Moreover, the key terms ‘experimental infection’ or ‘challenge infection’ primarily identify studies in animals.

Based on references in Pubmed since 1900, Roestenberg et al. estimated that altogether 23,307 volunteers have been experimentally infected with different pathogens [49]. Infection models with the largest numbers of volunteers were Rhinovirus (5760), influenza virus (3540) and *Plasmodium falciparum* (2650) followed by ETEC (1215), *Vibrio cholerae* (1210), *Salmonella typhi* (1000), RSV (1000), *Shigella spp* (1000), Norovirus (810), *Lactobacillus spp* (800), *Streptococcus pneumoniae* (790), *Hae-mophilus duceyi* (550), Dengue virus (520), Francisella tularensis (500), *Neisseria lactamica* (310), *Plasmodium vivax* (300), *Campylobacter jejuni* (260), *Cryptosporidium spp* (260), *Necator americanus* (250), BCG (140), *Neisseria gonorrhoeae* (140), *Giardia lambia* (120), *Helicobacter pylori* (80), *Salmonella paratyphi* (40) and Parvovirus B19 (12) [49].

Calculations of Evers et al. are slightly deviant estimating more than 41 116 healthy human volunteers who were intentionally exposed to infectious pathogens in clinical research studies up to the early 2000s. Based on references identified in clinicaltrials.gov, an estimated...
number of 4011 volunteers were experimentally infected between 2010 and the present day, but this may be an underestimate because a small number of aetiological agents were queried and clinicaltrials.gov is not an exhaustive database [1].

Based on references identified in Pubmed since the 1950s, we estimate that 3500 volunteers participated in vaccine efficacy studies which (i) measured disease as an endpoint; (ii) included unvaccinated ‘infection controls’; (iii) were randomised and double-blinded; (iv) reported that volunteers consented after being informed. About half of these volunteers were recruited for influenza (1035) and malaria (776) challenge trials.

The establishment of challenge centres for influenza and malaria challenge trials permits the assumption that such model infections will be routine methods for the evaluation of vaccine candidates and drugs [50–52]. In respect to malaria, successful employment of CHMI trial centres in the tropics, particularly sub-Saharan Africa, will be one of the most critical advancements for translational malaria research [53–55]. Present-day practices in experimental infections in vulnerable populations, particularly in Sub-Saharan Africa, where many trial participants live in extreme poverty, vis-à-vis experimental infections in high-income countries, where trial designs typically emerge, have to be evaluated and may trigger further essential discussions amongst funders, clinical researchers and local ethics committees. These discussions will ultimately contribute to superior ethical guidelines that permit acceleration of urgently needed medical interventions in the future.

Future regulations of challenge experiments must consider issues of justice in international research as addressed in paragraphs 20 and 34 of the Declaration of Helsinki. These include meeting the health priorities of vulnerable populations in clinical trials and post-trial provisions for access to interventions that turned out to be beneficial [56]. Challenge studies should only be carried out in a adequately equipped and adequately resourced facilities and when appropriate insurance schemes or equivalent measures are in place to compensate the participants should something go wrong. This may be self-evident, but these measures could be problematic to achieve in low-income settings, or when the national legislation lacks explicit/stringent requirements for insurance.

Conclusions

Human infection models are ideal to provide insight into host-pathogen interactions and offer excellent tools to evaluate the safety and efficacy of drugs or vaccine candidates, because confounding factors can be reduced to a minimum and because the required time of investigation is comparatively short and does not depend on incidence. Moreover, negative findings can illuminate and widen the scientific horizon [57]: By the early rejection of candidates or dose regimens that do not demonstrate the ability to protect challenged subjects under highly controlled conditions, the efficiency of drug and vaccine development may be improved, and time as well as costs can be saved [46]. Sample size calculations for trials in naturally exposed individuals can be facilitated, and human subjects in field trials, which often include vulnerable groups, will only be exposed to the most promising candidates.

It is implicit, but perhaps it should be stated explicitly: groups traditionally seen as vulnerable in research, such as children and those unable to give informed consent, should be systematically excluded from experimental infections. Corollary to this, it should go without saying that pregnant and lactating women should also be systematically excluded. As it appears that current ethical guidance remains vague or overly general when it comes to the specific risk: benefit assessment for research implying experimental infections in human volunteers, a call for more targeted ethical guidelines in this field of research is appropriate.

Always, the history of challenge studies should be recalled and the Willowbrook discussion should be kept alive: trial participants must provide adequate informed consent, no volunteer should be unnecessarily exposed to pathogens, and risks have to be carefully evaluated, minimised and justified. However, with an adequate degree of control and regulation, challenge models can be a great chance and benefit for the development of medical interventions to fight infectious diseases.

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