The Red Cross Gamma Globulin Field Trials (1951-1953)

Purpose

- Primary research question:
  - Does the prophylactic injection of pooled human immune globulins prevent paralytic poliomyelitis?

- Primary outcomes:
  - Paralytic polio based on clinical examination

- Perceived clinical importance:
  - No means existed for the prevention of polio.

Background and Context

- By the 1950s, Western countries experienced large, seasonal polio epidemics. This was because of improved hygiene and sanitation. Rather than immediately exposure to poliovirus after losing maternal antibodies, children became susceptible to infection at later ages. Infection during older ages resulted in more severe disease, including paralysis and death.

- In North America, polio epidemics were a public health issue of great concern. The National Foundation for Infantile Paralysis (NFIP) was a private foundation that accepted donations established by President Franklin D. Roosevelt, a polio victim. Accordingly, US research prioritized polio. Numerous scientific advances were made during the 1930s - 1950s.
  - The NFIP would later become known as the 'March of Dimes'.
  - The NFIP created a model of grant funding researchers that allowed 'indirect costs' to not over-burdened the administrative costs of managing grants.[1]

- In the 1940's, scientists at Harvard separated the proteins in blood,[1] and discovered immune globulins that could prevent infections. Evidence suggested neutralizing antibodies were protective against polioviruses in animals,[2] and there were several instances during epidemics of human convalescent serum or whole blood given to passively immunize children.

- Tests of gamma globulin suggested that it had many times greater concentration of antibodies compared to plasma, but an early human trial in 1944, was denied because the American Red Cross, the major supplier of blood products, would not

release gamma globulin since it was impractical in terms of staffing and not a priority during wartime.[1] Paradoxically, polio was a concern for the US military because of cases among troops stationed abroad.[3] Other arguments against a trial were a lack of consensus on its scientific plausibility, debate on the pathogenesis of polio, the scarcity of gamma globulin, and the utility of passive immunization.[1]

- During the post-war 'baby boom' era, polio was feared.[4] Cases continually increased, and the March of Dimes kept polio in the public eye.[1] Gamma globulin was given for measles and hepatitis prophylaxis and interest for the treatment of polio remained. Early tests of gamma globulin in humans, however, were not rigorously designed therefore it was difficult to estimate efficacy.[2;5]

- Although a polio vaccine was desired, views on its feasibility were mixed.[2] A major proponent of passive immunization against polio by gamma globulin was William Hammond,[3] from the University of Pittsburg. An enthusiastic researcher,[1] Hammond advocated a massive trial to examine the effectiveness of gamma globulin to prevent paralytic polio. In 1950, Hammond's proposal for a trial was not supported by the NFIP or peers also working on polio research at the time (Sabin, Enders, Salk).[1;6]
    - Reasons against the trial included the use of placebo controls, the negative responses from parents whose children received placebos, and fears that injections would provoke paralysis.[1]

- By 1951, further evidence was presented indicating gamma globulin could work. Even though it might not be an ideal prevention method, it would further help to advance an understanding of the pathogenesis of polio. The now formalized Committee on Immunization recommended Hammond carry out a pilot trial of 5000 children.[1;6]

Date and Place Conducted

- The 1951 pilot study was carried out in Utah county, Utah. The site was chosen based on existing morbidity data, population size, and trends suggesting an impending epidemic of sufficient size.[5]

- The larger trial in 1952 was carried out in counties in Texas, Iowa and Nebraska.[7] Counties in Texas were selected after it was determined that an epidemic of sufficient size had begun. Counties in Iowa and Nebraska were selected after the closure

of clinics in Texas and as it was determined that a large number of cases would occur in coming weeks.[7]

Principal Investigators

- William Hammond, Lewis Coriell, Paul Wehrle, Christian Klimt, and Joseph Stokes

Sponsored by/source of funding

- The National Foundation for Infant Paralysis

Size and Design

- A randomized, double-masked, placebo-controlled trial

- Number of participants: 33,137 children in Texas, 15,868 in Iowa and Nebraska[7]

- Participant characteristics:
  - Children were eligible if aged 2 to 11 years.

- Randomization and intervention
  - Children were given either gamma globulin or placebo based on random selection (via draw of a black or white colored ball) of pre-packaged vials with only serial numbers labeling them. Knowledge of the serial numbers and intervention was kept only by two clerks and held at the NFIP headquarters.
  - Children without either injection would be followed as an additional control group.
  - A control solution of gelatin, known to be safe for injection was created in the same color and viscosity of the gamma globulin.
  - The Red Cross supplied gamma globulin, prepared from blood collections during World War II from thousands of blood donors throughout the country.[8] Dose of gamma globulin was given by weight and ranged from 5 to 12 cc. Following the pilot study, a disposable syringe was developed (Becton-Dickinson) for faster operations.[7]
  - To prevent use of gamma globulin by physicians outside of the trial, the American Red Cross only authorized the release of gamma globulin to those involved in the trial.[7]

Issues Encountered During the Trial

- The pilot test in Utah was designed to enrolled 5,000 children, based on sample size calculations that gamma globulin would reduce the rate of paralytic polio by 50% and based on surveillance estimates of prior rates of polio expected in Utah.[5] The pilot test was estimated to be 1/10 the size of a trial needed

to provide conclusive evidence.

- Investigators prepared for the massive effort of injecting children at multiple sites across multiple states. They publicized community education and trial participation in newspapers and by communications with state health departments.[5] They described the steps taken for taking individual parental consent.

- Within 3 days, the investigators enrolled 5,768 children aged 2-8 years and stopped enrollment after exhausting the supply of gamma globulin. The pilot test was met with great enthusiasm. According to investigators, "The reaction of the public during and after the clinic period was astonishing".[5] Participation in the trial went against conventional wisdom of keeping children away from large groups during polio epidemics.

- Results of the pilot study were promising, though they deemed them not statistically significant: 1 polio case occurred among the gamma globulin group (2,871 children), 5 cases occurred among the 2,860 children in the placebo group. This was compared to 12 cases among 6,800 children without any injection during the same time period. The data also suggested that severity of paralysis was less severe with gamma globulin and there were few adverse events associated with injection. Given the pilot test success they recommended continuation "until a significant answer could be obtained".[5]

- It was later rumored that in Houston during the trial, some doctors gave patients gamma globulin outside of the protocol, believing that they were helping their patients.[1]
  - On this subject during an interview, Dr. Thomas Rivers, a preeminent virologist explained that there was nothing a researcher could do about this: "When all is said and done, a family will trust and believe the family physician more than it trusts … a scientist who is connected with …an institution…. You don't raise hell with the family doctor, no matter how justified you think you may be, because if you do, you quickly find yourself in trouble with the public." [1]
  - Nothing appeared to be published referring to protocol violations.

Findings

- Preliminary results showed 26 cases of paralytic polio occurred in the gamma globulin group and 64 cases occurred in the gelatin group, a difference considered statistically significant.[9] Final results reported of the total 104 cases of paralytic polio

over a 13-weeks, 93 were in the placebo group and 31 in the gamma globulin group ($X^2 = 16.99$, $p<0.001$)[10]

- Among paralysis cases occurring within seven days of inoculation, severity and extent of paralysis was less among cases receiving gamma globulin compared to those receiving gelatin.[9]

- Later analysis of trial results showed that gamma globulin was 80% effective for five weeks and that gamma globulin did not interfere with acquiring immunity from natural infection.

Impact

- The results of the trial were met with enthusiasm of the public and the press and heralded as the first effective means of preventing polio.[8] An accompanying editorial called the "55,000 children who participated in this research problem dynamic proof of the confidence of the American people in our system of medicine and medical research."[11]

- The disadvantages of gamma globulin were noted as the short duration of protection, the need for re-injection during epidemics and the unknown optimal time for injections.[12]
  - The goal of a vaccine against polio was still mentioned with gamma globulin providing only temporary immunity.
  - It was noted that the number of children and adolescents at risk for polio far outweighed the availability of gamma globulin.
- In the years following the trial, confusion existed in its effectiveness and in the appropriate distribution of gamma globulin.[13]
  - The US Public Health Service (USPHS) and the NFIP differed in their views for how gamma globulin should be used.[2] The USPHS initially wanted to restrict use to family contacts. The NFIP wanted community-wide use to prevent epidemics. Hammond argued against community-wide use given its limitations.[6]
  - In the year after the trial, the effectiveness of gamma globulin was questioned after its use during mass injections during outbreaks.[14] It was also noted that supplies were insufficient.[6]
  - A US panel reported that mass injections failed, that in most cities it had been given after the epidemic had peaked, and that it could not be shown that gamma globulin altered the course of the epidemic.[6] Hammond protested and filed a minority report. The report created "a public fiasco" in which the NFIP tried to explain that

inconclusive evidence did not equate to *evidence against* its effectiveness.[6;13]

- Later, a meeting of international experts called all existing polio control efforts a "complete failure" while they made recommendations on disease control and quarantine. Hammond presented additional analyses that showed its effectiveness. They condemned the use of gamma globulin for mass distribution but recommended it could be given to close contacts of cases.[1;15]
- Meanwhile, in the US some made calls for mandatory blood donations to ensure that enough gamma globulin would be available for mass immunizations against polio.[16]
- It was believed that the 'family contact' use of gamma globulin did not work because children in infected households had been given it too late after they had already been exposed.[13]

o Meanwhile, the first vaccine trial was planned by Dr. Jonas Salk and would enroll 500,000 to 1,000,000 children.[13] During the trial the use of gamma globulin was restricted to geographic areas not involved in the Salk trial.[6] Popular and medical opinion shifted their support from gamma globulin to the new polio vaccine.

Unresolved issues

o Immune globulin remains an option of preventing disease through passive immunization.
o It remains an issue of discussion for what constitutes the appropriate choice of a control group during the testing of new vaccines and therapeutics.[6]

Summary

The gamma globulin field trials (1951-1953) were among the first large randomized, double-masked, placebo-controlled trials. They showed the effectiveness of injected immune globulin for the prevention of paralytic polio among children during epidemics. Injecting 50,000 children over several days in multiple locations in the US, they were an achievement in logistics, community mobilization, and coordination and communication among public health researchers and the public. However, the success of the trial was overshadowed by (1) differences between trial results and effectiveness as an intervention in observational data, (2) conflicting views on the correct plan of distribution, (3) scarcity of gamma globulin as a product of limited supply but great demand, and (4) the Salk polio vaccine which soon after was found to be a more effective intervention.

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