Inactivated Polio Vaccination Using a Microneedle Patch

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ABSTRACT SUMMARY
Microneedle patches were designed to simplify delivery of inactivated polio vaccine (IPV) and increase vaccine immunogenicity in support of global polio eradication. These patches were shown, for the first time, to be safe and effective in the rhesus macaque. We also showed that slow release of IPV in the skin increased vaccine immunogenicity compared to bolus dosing. In this way, IPV vaccination using a microneedle patch may facilitate mass vaccination and increase vaccine immunogenicity.

INTRODUCTION
As a result of extensive mass vaccination campaigns, poliovirus has been eliminated in much of the world. Current polio vaccination strategies utilize the oral polio vaccine (OPV). Unfortunately, this live-attenuated vaccine can revert to its virulent form, which causes disease. Therefore, complete eradication of polio will require a switch from OPV to the inactivated polio vaccine (IPV), which carries no risk of polio transmission. Because IPV is currently delivered by hypodermic injection, IPV vaccination presents many challenges.

Microneedle patches contain micron-scale needles that can penetrate the upper layers of skin to deliver therapeutics. Microneedle patches can aid in polio eradication by reducing costs and easing logistics, especially during vaccination campaigns. This delivery technique minimizes vaccine wastage by employing a single-dose presentation and removing the need for vaccine reconstitution. Additionally, microneedles can be administered by minimally trained personnel and the needles dissolve fully in the skin, leaving no sharps waste. Microneedle patches have not been studied before for polio vaccination.

Controlled release of antigen is another strategy to increase vaccination coverage by reducing the number of required doses or through antigen sparing. This strategy has not been studied before for polio vaccination.

EXPERIMENTAL METHODS
Microneedle patches were fabricated by sequential casting of an antigen solution followed by a polymeric matrix solution onto a silicone micromold and allowed to dry. Enzyme-linked immunosorbent assay (ELISA) was used to determine IPV dose per patch.

Rhesus macaques were vaccinated with a human dose of IPV using either intramuscular injection or microneedle patches (n=4 per group). After 8 weeks, all animals were given a booster using the same route and dose as the initial vaccination. Blood was collected weekly and polio-specific neutralizing antibody titers were measured by microneutralization assay.

For the controlled-release study, Wistar rats received an intradermal injection of type 2 IPV every day for seven days. Different profiles of antigen dosing were delivered to each group of rats, while maintaining the total dose (0.8 DU) administered constant. Blood was collected every 2 weeks for 8 weeks and polio-specific neutralizing antibody titers were measured.

RESULTS AND DISCUSSION
Microneedle patches were fabricated as 10 x 10 arrays of pyramidal needles, seen in Figure 1. Insertion into pig skin showed that the needles were strong enough to penetrate the skin. ELISA testing confirmed loading of a full IPV dose in the patches and that the dose was delivered into the skin upon needle dissolution. Microneedles were inserted by thumb into the skin without need of an applicator.
While microneedle patches have been studied before for other vaccines, polio vaccination has not been tested before. We therefore vaccinated rhesus macaques with a full human dose of IPV types 1 and 2 with a prime dose and a booster dose 8 weeks later. The neutralizing antibody response after microneedle patch vaccination closely matched that of the intramuscular vaccination group, showing no statistically significant differences (Fig. 2). Following the booster, all the animals exhibited protective antibody titers for type 1 and 2 poliovirus by week 12. No animals in either vaccination group exhibited any systemic or local adverse events or safety concerns.

In humans, a single vaccination only provides protection to about 50% of recipients, and three doses are necessary to achieve 95% seroconversion. To improve vaccine immunogenicity and increase seroconversion rates, we hypothesized that altering the kinetics of antigen presentation in the skin, we could improve vaccine immunogenicity. In this preliminary study, we delivered IPV type 2 by (a) bolus injection on day 1, (b) pulsatile dose (1/2 dose on days 1 and 7), or (c) a constant dose (1/7 dose daily for seven days). Blood was collected every 2 weeks for 8 weeks. After 2 weeks, neutralizing antibody titers were similar for the bolus and pulsatile groups, but were significantly higher for the constant dose group (Fig. 3). The seroconversion rates (i.e., titers > 3) were 20% for the intramuscular bolus group, 40% for the intradermal bolus injection, 40% for the pulsatile group, and 100% for the constant group. We are currently investigating how other release profiles will affect vaccine immunogenicity.

CONCLUSION
We used a microneedle patch to safely and effectively deliver IPV to rhesus macaques. Using controlled vaccine release, we showed significantly increased vaccine immunogenicity after constant vaccine dosing for one week, achieving 100% seroconversion after a single dose in rats. These findings suggest that IPV vaccination using a microneedle patch formulated for controlled release may aid in vaccination in poliovirus outbreaks and provide improved immunity after a single vaccination.

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Figure 1: A microneedle patch containing IPV. The inset shows a single needle at higher magnification.

Figure 2: Neutralizing antibodies to types 1 and 2 poliovirus in rhesus macaques after vaccination by intramuscular injection and microneedle patch showing no statistical difference between the two vaccination groups.

Figure 3: Neutralizing antibodies to type 2 poliovirus after skin vaccination in rats using different dosing protocols. (ANOVA; p < 0.001; *=p<0.01)