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Effect of jet injection on infectivity of measles, mumps, and rubella vaccine in a bench model

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ABSTRACT

Disposable-syringe jet injectors (DSJIs) with single-use, auto disable, needle-free syringes offer the opportunity to avoid hazards associated with injection using a needle and syringe. Clinical studies have evaluated DSJIs for vaccine delivery, but most studies have focused on inactivated, subunit, or DNA vaccines. Questions have been raised about possible damage to live attenuated viral vaccines by forces generated during the jet injection process. This study examines the effect of jet injection on the integrity of measles, mumps, and rubella vaccine (MMR), measured by viral RNA content and infectivity. Three models of DSJIs were evaluated, each generating a different ejection force. Following jet injection, the RNA content for each of the vaccine components was measured using RT-qPCR immediately after injection and following passage in Vero cells. Jet injection was performed with and without pig skin as a simulation of human skin. There was little to no reduction of RNA content immediately following jet injection with any of the three DSJIs. Samples passaged in Vero cells showed no loss in infectivity of the measles vaccine following jet injection. Mumps vaccine consistently showed increased replication following jet injection. Rubella vaccine showed no loss after jet injection alone but some infectivity loss following injection through pig skin with two of the devices. Overall, these data demonstrated that forces exerted on a live attenuated MMR vaccine did not compromise vaccine infectivity. The bench model and protocol used in this study can be applied to evaluate the impact of jet injection on other live virus vaccines.

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1. Introduction

Percutaneous injuries and sharps disposal are concerns during immunization activities. The CDC estimates that 385,000 sharps-related injuries occur annually among healthcare personnel in the United States [1]. Additionally, needle reuse in developing countries remains problematic; an estimated 40% of patients risk exposure from reused needles [2,3]. Auto disable, single-use syringes substantially reduced needle reuse; however, safe sharps disposal practices are a continual demand on immunization activities. Disposable-syringe jet injectors (DSJI) offer a needle-free alternative to standard injections.

Jet injectors have been used for the delivery of vaccines since the 1930s and have delivered hundreds of millions of doses of live attenuated vaccines [4,5]. However, multiple-use nozzle jet injectors potentially exposed vaccinees to blood-borne pathogens from cross-contamination of the injection nozzle and are no longer recommended for vaccinations [4–7]. DSJIs have single-use syringes preventing cross-contamination between recipients. Vaccination by DSJI has several benefits including reduction of needle stick injuries and sharps waste and the potential for improved acceptability, coverage, and efficiency of vaccine delivery.

Abbreviations: CDC, centers for disease control and prevention; CRS, congenital rubella syndrome; DSJI, disposable-syringe jet injector; MMR, measles, mumps, and rubella vaccine; MeV, measles virus; MuV, mumps virus; RuV, rubella virus; WHO, World Health Organization.

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The WHO estimates that global immunization coverage for measles containing vaccine in 2013 was 84%, with many countries still well below the recommended 95% level required to interrupt endemic measles transmission [8]. Measles is a severe childhood illness which resulted in an estimated 122,000 deaths worldwide in 2012, mostly affecting children under the age of 5 [9]. In 2000, the WHO recommended the introduction of rubella into childhood immunization schedules and coupled rubella control activities to current measles immunization programs [10]. Though rubella is considered a mild rash disease, infection of a woman during pregnancy can lead to congenital rubella syndrome (CRS) which is associated with miscarriage, stillbirth or serious sequelae in the neonate [11–13]. Though rubella, like measles, has been eliminated in the United States, the WHO estimates that there are 110,000 cases of CRS annually [14,15].

The use of DSJIs may provide an opportunity to improve global immunization programs by providing a needle-free alternative. DSJIs create a liquid stream that penetrates the skin by forcing the vaccine through a small orifice at a high speed [4,5]. Studies of DSJI in both animal models and clinical trials support the non-inferiority of DSJI vaccination compared with needle and syringe [5,16–20]. The majority of these studies evaluated inactivated, subunit, or DNA-based vaccines, though a recent clinical study found that immune responses generated following DSJI delivery of Bacille Calmette–Guérin (BCG) vaccine, a live attenuated bacterial vaccine for tuberculosis, was also non-inferior to needle and syringe delivery [16–19,21–25]. Another recent study assessed responses to the live attenuated measles, mumps, and rubella (MMR) vaccine [21]. The DSJI vaccination did not meet the criteria for non-inferiority for measles and mumps, raising questions about possible adverse effects of mechanical forces during injection on vaccine stability [21]. This study evaluated the integrity of MMR vaccine after jet injection by measuring RNA content and infectivity.

2. Materials and methods

2.1. Cells and vaccine

Vero cells (ATCC, CCL-81) were grown in 10% Dulbecco Modified Eagle Medium (DMEM) (Gibco; Grand Island, NY) supplemented with penicillin-streptomycin and L-glutamine (Gibco; Grand Island, NY). The Serum Institute of India kindly provided MMR trivalent and monovalent measles (MeV) and rubella (RuV) live attenuated vaccines.

2.2. Preparation of pig skin

Skin overlying the caudal margin of the ribs in the region of the flexed elbow was harvested from a 6-month old Yorkshire pig. This region was chosen because of histological similarity to human skin. Pig skin has a comparable thickness in the epidermis as human skin with similar dermal/epidermal ratios as human skin. Additionally, pig skin is structurally similar to human skin in the distribution of blood vessels and the staining pattern of skin antigens [26]. Adipose tissue was removed from the skin by dissection to avoid vaccine retention.

2.3. Jet injection

Ten-dose vials of MMR were reconstituted in pre-warmed, serum-free DMEM supplemented with penicillin-streptomycin. Triplicate samples were reserved for testing as pre-injection samples. The DSJIs used were the PharmaJet Stratis® 0.5-ml Needle-Free Injection System, referred to as Stratis®, and the first-generation PharmaJet system referred to as G1 (Fig. 1) (PharmaJet; Golden, CO, USA, www.pharmajet.com). The G1 system consisted of two injectors, the G1-blue—designed for adults and children aged

Fig. 1. PharmaJet DSJIs used for evaluation of injection of MMR. The DSJIs used were the PharmaJet Stratis® 0.5-ml Needle-Free Injection System, referred to as Stratis®, and the first-generation PharmaJet system, referred to as G1 (PharmaJet; Golden, CO, USA, www.pharmajet.com). The G1 system consisted of two injectors, the G1-blue—designed for adults and children aged 2 years and older, and the G1-purple—designed for infants and children up to 2 years old. The Stratis® injector is the current US Food and Drug Administration approved PharmaJet device.