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# Supplementary Materials for

## A gastric resident drug delivery system for prolonged gram-level dosing of tuberculosis treatment

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**The PDF file includes:**



**Other Supplementary Material for this manuscript includes the following:**

(available at www.sciencetranslationalmedicine.org/cgi/content/full/11/483/eaau6267/DC1)

Table S4. Individual subject-level data for Figs. 2 (B to G) and 3 (C and D) and figs. S3A, S4A, S5B, S6, S7 (B and C), S7 (E and F), and S8 (Excel format).
Data file S1 (.STL format). In vitro design of 3D stomach model.
Data file S2 (.pdf format). Field questionnaire study to inform mode of administration.
Data file S3 (Microsoft Excel format). Sensitivity analysis of health and economic model.

**Supplementary Materials**

**Materials and Methods**

Manufacturing of the gastric resident system (GRS)

The assembled GRS consists of a superelastic nitinol wire as the retention frame upon which drug pills are strung with a retainer and tubing at the ends of the device. Nitinol wire (Fort Wayne Metals), with diameter of 0.59 mm and phase transformation at 37°C, was wrapped around a custom fixture to create a helical shape and secured in place using steel screws. The nitinol-fixture assembly was placed in a furnace at 500 °C for 15 minutes and then quenched in water at room temperature for 20 minutes. The nitinol was unwrapped from the fixture, ready for pills to be added.

Doxycycline hyclate was purchased from MedChem Express LLC. Isoniazid was purchased from Sigma-Aldrich Corporation, and moxifloxacin was purchased from ArkPharm, Inc. Rifampicin, ethambutol, and pyrazinamide were purchased from Hangzhou Hysen Pharma Co. Ltd. Drug pills were made using the following protocol: The drug was first added to the vinylpolysiloxane (VPS) base (Zhermack Elite Double 22) and mixed at 3200 rpm for 30 seconds using a SpeedMixer DAC 150.1 FVX-K (FlackTek Inc.). To prevent drug loss, we ensured that all the drug was mixed into the matrix before proceeding. After 2 minutes of cooling, poly(ethylene glycol) (PEG) molecular weight 3500 (Sigma-Aldrich Corporation) or molecular weight 400 (Sigma-Aldrich Corporation) was added and mixed into the drug-VPS base matrix using the SpeedMixer at 2700 rpm for 30 seconds. After 2 minutes of cooling, the VPS catalyst (Zhermack Elite Double 22) was added and mixed using the SpeedMixer at 1750 rpm for 30 seconds. Drug loading percentages were determined relative to the final cured silicone mixture weight: doxycycline hyclate (32%), isoniazid (32%), ethambutol (25%),

pyrazinamide (30%), moxifloxacin (20%), and rifampicin (54%). The viscous uniform blend was poured into a disposable polystyrene Petri dish (VWR), and individual pills were extracted using a 4 mm Miltex disposable biopsy punch (Integra). A 0.5 mm biopsy punch (Electron Microscopy Sciences) was used to core out a hole in the center of the drug-VPS pill to allow the nitinol wire to pass through.

The pills were spray-coated in a DKE stainless steel pan (ERWEKA GmbH) with a 9.5 L capacity attached to an AR 403 drive unit (ERWEKA GmbH). The Eudragit RS 100 (Evonik Corporation) solution was prepared as recommended by Evonik *(60)*. Briefly, the Eudragit RS 100 pellets were dissolved in 50% of a diluent mixture, composed of 342.90 grams of acetone (Sigma-Aldrich Corporation), 514.20 grams of isopropanol (Sigma-Aldrich Corporation), and 42.90 grams of water. In a separate beaker, an excipient mixture of talc (<10 um particle size from Sigma-Aldrich Corporation), triethyl citrate (Sigma-Aldrich Corporation), and red dextrose food dye (CK Products) was homogenized into the remaining 50% of the diluent mixture for 15 minutes. The excipient mixture was then poured into the beaker containing the Eudragit solution and stirred. Lastly, the spray suspension was passed through a 500 µm sieve (McMaster-Carr). To prepare a poly(Ɛ-caprolactone) (PCL) spray solution, PCL molecular weight 45,000 (Sigma-Aldrich Corporation) was added to acetone at 5% weight per volume. The solution was then placed on a hot plate with a stir bar at 50 °C and 200 rpm. The PCL pellets started to fully dissolve and form a homogenous solution after one hour. The spray gun used was a 0.8 mm nozzle, handheld Master E91 airbrush (TCP Global) attached to beakers in the kit with a spray volume of 18 mL and held at a 90° angle to the rotating pan with a 7 cm distance from its outer diameter. The coating pan was tilted at a 45-degree angle for all the formulations and rotated at 70 rpm for the Eudragit RS 100 solution and at 300 rpm for the PCL solution. A heat gun (Uline)

was placed directly underneath the coating pan and set to 50 °C to induce film formation on the pills sprayed with Eudragit RS 100. The Eudragit RS 100 sprayed pills were dried for 2 hours after spraying in a circulating air oven set at 40 °C. The typical batch size for spraying was 100 pills. It took 120 minutes to spray pills with 300 mL of Eudragit RS 100, and it took 100 minutes to spray pills with PCL.

The nitinol wire was inserted into the 0.5 mm hole of the coated drug-VPS pills, and after the desired loading was achieved, each end of the nitinol wire was crimped using a pair of pliers. PCL molecular weight 37,000 (Sigma-Aldrich Corporation) pellets were then pressed into two 3-inch (76.2 mm) long pieces of Tygon tubing (Inner Diameter X Outer Diameter: 4.76 x 6.35 mm), which was obtained from McMaster-Carr. The end of each tube was then filled with Med3-4213 silicone adhesive (NuSil), followed by a 6.35 mm stainless steel ball bearing. Once completely packed with the pellets, the tubes were heated at 100 °C to melt the PCL using a heat gun. Each crimped end of the nitinol was then slowly inserted into the molten PCL and set into place as the PCL cooled at room temperature to solidify around the nitinol wire. More silicone adhesive was used to seal the free ends of the tubes at both ends of the device

<u>In vivo evaluation of the immediate release and gastric resident system (GRS)</u>

All animal experiments were performed in accordance with protocols approved by the Committee on Animal Care at the Massachusetts Institute of Technology and as previously described *(30, 31, 61, 62)*. To assess the oral pharmacokinetics of immediate release formulations and gastric retentive drug delivery devices, we administered them to a large animal model (30-75 kg Yorkshire pigs). This model was chosen because its gastric anatomy is similar to that of humans and is widely used in evaluating devices in the GI tract *(36, 63)*. Animals were fed daily in the morning and in the evening with a diet consisting of pellets (Laboratory mini-pig

grower diet, 5081), in addition to a midday snack consisting of various fruits and vegetables. The pellets consisted of ground oats, alfalfa meal, wheat middlings, soybean meal, dried beet pulp, salts, and other micronutrients.

The immediate release formulation was prepared by weighing and filling 100 mg of doxycycline hyclate in a "00" gelatin capsule (Purecaps USA) 15 minutes prior to dosing. Prior to dosing, the pigs were sedated with Telazol® (5 mg/kg IM), xylazine (2 mg/kg IM), and atropine (0.04 mg/kg IM), intubated, and maintained with isoflurane (1 to 3% inhaled). Immediate release and GRS formulations were deployed in the stomach via an endoscopic guided overtube (Inner Diameter X Outer Diameter: 16.7 x 19.5 mm) from US Endoscopy. The overtube was removed once the devices were administered. For evaluation of the safety and residence time of the gastric retentive drug delivery devices, the animals were clinically assessed twice a day for evidence of GI obstruction including inappetence, abdominal distension, lack of stool, and vomiting. Additionally, the animals were evaluated radiographically every day 3-4 days for evidence of GI obstruction and/or perforation. Tissue samples were collected before and after the device was placed in the stomach for histopathological analysis, and macroscopic images were taken once the device was retrieved to study any possible mucosal damage. Blood samples were obtained from an external mammary vein on the ventral surface of the pig at indicated time points. Serum samples were separated from blood by centrifugation (3220 rpm, 10 min at 4 °C) and were stored at -80 °C for further analysis.

Manufacturing and evaluation of the retrieval device

The retrieval device was constructed using three 4.76 mm diameter x 4.76 mm length cylindrical neodymium magnets with pull force of 10.14 Newtons (K&J Magnetics, Inc.) and an Allegro A1324 linear Hall effect sensor (Modern Device), all housed in a 1-meter long Tygon tube (Inner

Diameter X Outer Diameter: 4.76 x 6.35 mm). The sensor and magnets were placed on one end of the Tygon tube, with the sensing face of the sensor bent at a 45-degree angle relative to the magnets. Each pin of the sensor was soldered to a 26-gauge, solid electrical wire (Adafruit Industries LLC) and covered in heat shrink tubing to avoid shorting the sensor. A thin layer of Med3-4213 silicone adhesive was applied at the tip of the outermost magnet to give the magnets a slight downward offset from the top surface of the tubing and keep the magnets of the retrieval device slightly separated from the magnet of the drug delivery device upon connection. An Arduino Pro Mini 328 (SparkFun Electronics) received the output of the Hall effect sensor and sent a text output to a serial-enabled liquid crystal display (SparkFun Electronics). When the magnets of the retrieval device connected with the magnet of the GRS, defined by a Hall effect sensor output that exceeded a given voltage threshold for at least one minute, the liquid crystal display showed the message "The magnets are connected." A 3.7 V lithium ion battery (SparkFun Electronics) powered the microcontroller circuit.

The stability of the Allegro A1324 Hall effect sensor was tested in air first and then after immersion in simulated gastric fluid, USP without pepsin (pH ~1.2; henceforth referred to as SGF). The sensing area of the insulated sensors was covered with two-part epoxy (Devcon). The insulated sensor was placed in 4 mL of SGF for 90 minutes and then removed. After this period, the sensors and a 4.76 mm x 4.76 mm cylindrical neodymium magnet were fixed in place, with 10 mm separating the sensing face of the sensor and the south pole of the magnet. The sensor voltage output was read and recorded via the Arduino integrated development environment serial monitor to compare with the voltage read prior to immersion in SGF.

For in vivo evaluation of the retrieval device interaction with the GRS, the animals were sedated, intubated, and maintained with isoflurane as described above. The GRS was first deployed in the

stomach via an endoscopic guided overtube, and radiographs confirmed placement of the device in the gastric cavity. The retrieval device was then inserted into the overtube without endoscopic guidance to demonstrate the ability of the Hall effect sensor on the retrieval device to detect the magnet on the GRS. Radiographs were captured of the retrieval device as it entered the gastric cavity, contacted the GRS as indicated on the liquid crystal display board, and successfully retrieved the GRS.

In vitro stomach model

A three-dimensional (3D) model mimicking the human stomach was designed in SolidWorks (Dassault Systèmes) and created to analyze feasibility of the delivery and retrieval of the GRS (data file S1). The 3D part was split into two halves and then printed on a Stratasys Objet30 3D printer. Polyethylene terephthalate (PETG) sheets from McMaster-Carr with 3.175 mm thickness were formed around the stomach halves using a heat gun. A band saw (Home Depot) was used to trim the excess material away, leaving the PETG half stomach with a 25.4 mm border. The outline of the stomach shape designed on SolidWorks was used to generate a custom gasket for sealing the two halves of the in vitro model together. Two of these gaskets were laser cut out of 1.59 mm thick silicon rubber sheets (McMaster-Carr) using a Universal Laser Systems VLS6.60 and then glued onto each of the stomach halves with cyanoacrylate (Krazy Glue). About every 5 cm, clearance holes for M6 bolts (McMaster-Carr) were drilled around the perimeter of both halves.

The nasal passage, pharynx, and esophagus were modelled out of a 0.6-meter long PETG tubing (Inner Diameter X Outer Diameter: 9.525 x 12.7 mm) from McMaster-Carr. The tubing was bent with a heat gun to form a 90-degree turn. To interface the tubing into one stomach half, a custom adapter was printed using a Formlabs Form 2 3D printer. The bottom end of the tubing

was heated with a heat gun and press fit into the adapter. The upper section of the stomach half was also heated using a heat gun and fitted with the other side of the adapter. The two halves of the stomach were aligned, and 13 M6 bolts were used to secure the halves together and make the stomach model water tight.

Drug release in vitro

Individual pills made of drug-VPS for doxycycline hyclate, isoniazid, ethambutol, pyrazinamide, moxifloxacin were used to evaluate long-term release kinetics in SGF. Pill formulations were incubated in a New Brunswick Innova 44 shaking incubator (Eppendorf) at 37 °C and 200 rpm in 50 mL of SGF for up to 28 days, with solution exchanges at specified time intervals. Drug concentrations were then analyzed using a High-Performance Liquid Chromatography (HPLC). Because of the lack of a validated HPLC method for evaluating isoniazid in SGF, water was used to study differences between isoniazid formulations. Three intact rifampicin devices were fabricated by loading 2 grams of drug into VPS pills. The devices were incubated in 500 mL of nanopure water for up to 26 days in a shaking incubator at 37 °C and 200 rpm, with media exchange at specified time intervals. Water was used as a solvent for the drug release study because rifampicin rapidly degrades in acid *(64)*. The drug concentrations samples were then measured on an Infinite M200Pro (Tecan) reader (absorbance, 475 nm) *(65)*.

High-Performance Liquid Chromatography

An Agilent 1260 Infinity II HPLC system (Agilent Technologies, Inc.) equipped with a Model 1260 quaternary pump, Model 1260 High Performance autosampler, Model 1260 thermostat, Model 1260 Infinity Thermostatted Column Compartment control module, and Model 1260 diode array detector was utilized as described previously *(30, 31, 62)*. Data processing and analysis was performed using OpenLab CDS ChemStation (Agilent Technologies, Inc.). All

solvents used were purchased from Sigma-Aldrich Corporation. For doxycycline hyclate, chromatographic isocratic separation was carried out on an Agilent 4.6x50 mm AdvanceBio RP-mAb SB-C8 analytical column with 3.5 µm particles, maintained at 55 °C. The optimized mobile phase consisted of 20 mM dipotassium phosphate buffer and acetonitrile (pH 6 adjusted with triethylamine) [60:40 (v/v)] at a flow rate of 0.85 mL/min over a 4 min run time. The injection volume was 5 µl, and the selected ultraviolet (UV) detection wavelength was 293 nm.
For isoniazid and pyrazinamide, chromatographic isocratic separations were carried out on an Agilent 4.6x150 mm ZORBAX Eclipse Plus C-18 analytical column with 5 µm particles, maintained at 30 °C. The optimized mobile phase consisted of 10 mM sodium dibasic phosphate buffer and acetonitrile (pH 6.75 adjusted with phosphoric acid) [95:5 (v/v)] at a flow rate of 1.00 mL/min over a 6 min run time. The injection volume for both drugs was 20 µl, and both drugs were analyzed using a UV detection wavelength of 238 nm.

For moxifloxacin, chromatographic separation was carried out on an Agilent 4.6x50 mm Poroshell 120 EC-C18 analytical column with 2.7 µm particles, maintained at 50 °C. The optimized gradient consisted of nano-pure water and acetonitrile starting at [95:5 (v/v)] at 0 minutes then ramping to [50:50 (v/v)] at 2.5 minutes and descending to [95:5 (v/v)] by 5 minutes. A constant flow rate was maintained at 1.00 mL/min, and a post-run of 1 minute was utilized. The injection volume was 5 µl, and the UV detection wavelength of 293 nm was selected.

For ethambutol, chromatographic separation was achieved using a method described previously *(66)*. A Waters 3.9x300 mm µBondapak C18 analytical column with 10 µm particles, maintained at 35 °C, was utilized in an isocratic elution method. The optimized mobile phase consisted of buffered nano-pure water (1.0 mM $Cu(II)SO_4$, 4 g sodium 1-heptanesulfonate,

titrated to pH 4.50 with 10 mM HCl) and tetrahydrofuran [75:25 (v/v)]. A constant flow rate was maintained at 1.50 mL/min for 15 minutes, and a post-run of 1 minute was utilized. The injection volume was 20 µl, and the ultraviolet (UV) detection wavelength of 260 nm was selected.

Liquid chromatography-tandem mass spectrometry

Drug concentrations in serum from in vivo experiments were analyzed using Ultra-Performance Liquid Chromatography–Tandem Mass Spectrometry (UPLC-MS/MS). Analysis was performed with a Waters ACQUITY UPLC-I-Class System aligned with a Waters Xevo–TQ-S mass spectrometer (Waters Corporation). Liquid chromatographic separation was performed on an Acquity UPLC Charged Surface Hybrid C18 (50mm × 2.1mm, 1.7 µm particle size) column at 50 °C. The mobile phase consisted of aqueous 0.1% formic acid, 10mM ammonium formate solution (Mobile Phase A) and acetonitrile: 10mM ammonium formate, 0.1% formic acid solution (95:5 v/v) (Mobile Phase B). The mobile phase had a continuous flow rate of 0.6 mL/min using a time and solvent gradient composition. For the analysis of doxycycline hyclate, the initial composition (100% Mobile Phase A) was held for 1 minute, following which the composition was changed linearly to 50% Mobile Phase A over the next 0.25 minutes. At 1.5 minutes, the composition was 20% Mobile Phase A. At 2.5 minutes, the composition was 0% Mobile Phase A and 100% Mobile Phase B, which was held constant until 3 minutes. The composition returned to 100% Mobile Phase A at 3.25 minutes and was held at this composition until completion of the run, ending at 4 minutes, where it remained for column equilibration. The total run time was 4 minutes. For the analysis of rifampicin, the initial composition (95% Mobile Phase A) was held for 0.5 minutes, following which the composition was changed linearly to 15% Mobile Phase A over the next 1.25 minutes. At 1.76 minutes, the composition was 0% Mobile Phase A and 100% Mobile Phase B, which was held constant until 3.25 minutes. The

composition returned to 95% Mobile Phase A at 3.50 minutes and was held at this composition until completion of the run, ending at 4.50 minutes, where it remained for column equilibration. The total run time was 4.5 minutes.

For both the analysis of doxycycline hyclate and rifampicin, the sample injection volume was 2.5 µL. The mass spectrometer was operated in the multiple reaction monitoring mode. The mass to charge transitions (m/z) used to quantitate doxycycline hyclate, demeclocycline hydrochloride, rifampicin, and rifapentine were 445.19>154.1, 465.13>154.09, 823.5>151.17, and 877.55>151.18, respectively. Sample introduction and ionization was by electrospray ionization (ESI) in the positive ionization mode. Waters MassLynx 4.1 software was used for data acquisition and analysis.

Stock solutions of doxycycline hyclate, rifampicin, internal standards (IS) demeclocycline hydrochloride and rifapentine were prepared in methanol at a concentration of 500 µg/mL. A twelve-point calibration curve was prepared in analyte-free, blank serum ranging from 1–5000 ng/mL. 100 µL of each serum sample was spiked with 200 µL of 250 ng/mL IS in acetonitrile to elicit protein precipitation. Samples were vortexed and sonicated for 10 minutes and centrifuged for 10 minutes at 13000 rpm. 200 µL of supernatant was pipetted into a 96-well plate containing 200 µL of nanopure water. Finally, 2.5 µL was injected onto the UPLC–ESI–MS system for analysis.

Questionnaire study in India

The study was approved by the following institutions and committees: 1) Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects, 2) the Institutional Ethics Committee of Maulana Azad Medical College and Associated Lok Nayak Hospital, Govind Ballabh Pant Hospital, and Guru Nanak Eye Centre, New Delhi, 3) the New Delhi

Tuberculosis (TB) Centre, 4) the Ethical Committee of Rajan Babu Institute for Pulmonary Medicine and Tuberculosis, New Delhi, 5) the National Institute of Tuberculosis and Respiratory Diseases, New Delhi, and 6) the State Tuberculosis Officer of New Delhi for Delhi District Tuberculosis Centres at Gulabhi Bagh, Nehru Nagar, and Safdarjung Hospital.

Copies of the questionnaires can be found in data file S2. The four approaches for improving adherence were chosen by incorporating both behavioral and technological interventions as described the literature *(1, 67)*. Three routes of administration are compatible with multigram dosing and deployment through the esophagus: 1) placing a nasogastric (NG) tube to deploy a GRS, 2) swallowing many capsules, and 3) drinking water-drug mixture (inspired by the recent developments in gastric resident hydrogels) *(34, 62)*. These options were presented to health care providers and patients with approximate volumes of the drug necessary. Emphasis on the need for these routes to be administered in a TB clinic was placed to maximize the efficacy of the directly observed treatment short course (DOTS) strategy.

The questionnaire for health care providers was written in English and given to the providers on paper to fill out in English. Participants provided written informed consent. The questionnaire for patients was administered orally in Hindi with interpreters from Operation Asha. The translation was prepared by Ms. Manju Bajiya at Operation ASHA. Patients provided oral informed consent prior to participating in the survey. The surveys for the health care providers and the patients were piloted in January 2017 in New Delhi and in Mumbai with the guidance and assistance of healthcare professionals at Operation ASHA and Safdarjung Hospital. Based on the pilot study, we revised the wording of some questions in both questionnaires and developed an application on an Android tablet to record questionnaire answers from the patient. We also added the use of props (a representative sterile NG tube, 30 “000” capsules, and a 2 L

water bottle) to communicate the three routes of administration to the patients participating in the questionnaire. From August 2017 to November 2017, we conducted the full study with the support of the Ministry of Health and Family Welfare of the Government of India and Operation ASHA. All health care providers who filled out more than 90% of the questionnaire were included in the analysis. All 300 patients who provided consent for the study were included in further analysis.

Economic model

The economic model was based on a conceptual framework developed by David Collins at Management Sciences of Health and applied in Kenya and the Philippines *(52, 53)*. It describes the current impact of a treatment interruption for drug-susceptible TB (DSTB) patients on morbidity and mortality as well as the estimated financial impact of that treatment interruption in New Delhi, India from 2013-2014. The data, assumptions, and economic calculations were derived from a global literature review, a review of the National Tuberculosis Control Program (NTP) data, and from an expert panel of doctors, pharmacists, and NTP staff from Philippines. India and the Philippines have a similar GDP per capita and cost per TB patient, so the Philippines data set was used for diagnostic and treatment costs *(68)*. The following key assumptions were used: 1) 3 months is the mean length of treatment before loss-to-follow-up (LTFU), 2) no patients are infectious with drug-sensitive TB at the start of the period because they have all completed the intensive phase of treatment, 3) 3 months is the average length of interruptions, 4) 10% of patients are treated in the private sector during the LTFU, 5) 10% of patients develop MDR-TB when treated in the private sector, 6) 10% of patients develop MDR-TB while untreated, 7) 70% of the MDR-TB patients return to the public sector for treatment after LTFU, 8) 70% of the DSTB patients return to the public sector for treatment after LTFU,

and 9) the number of patients per month infected by active LTFU patients is 0.1. We conducted sensitivity analysis for these 9 parameters and included these in data file S3.

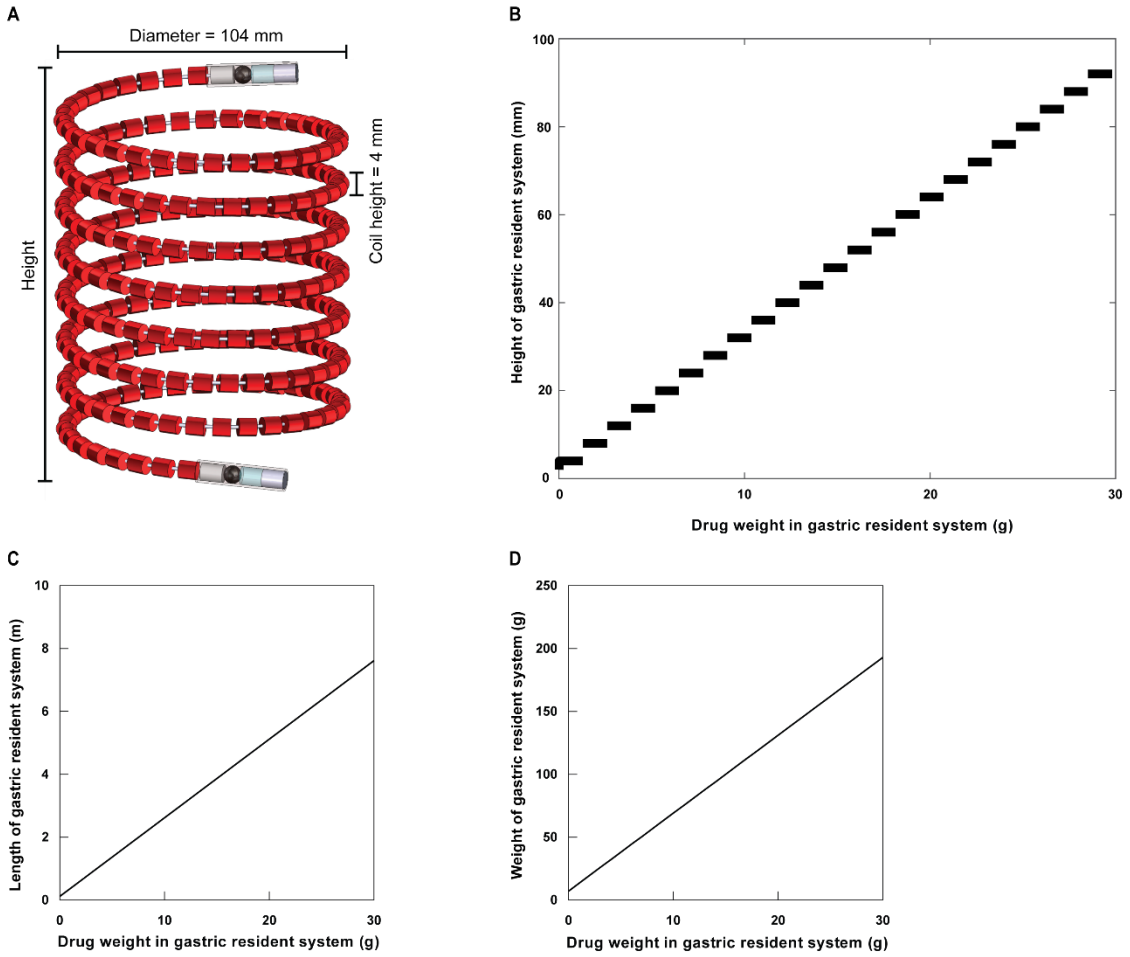



**Fig. S1. Physical parameters of the GRS as the drug weight increases. (A)** Diagram of the GRS and plot of height of device versus drug weight. The coil height is fixed at 4 mm due to the size of the measured drug pill height, and the diameter of the overall GRS is kept constant at 104 mm based on the size of the nitinol fixture (n=3). **(B)** The calculated height of the GRS as a function of the drug weight, calculated by the number of pills that can fit on a single coil based on measurements of the pill height and diameter of the GRS. The number of coils is discrete; between a certain range of drug weight, the height of the device will remain the same. **(C)** The

calculated overall end-to-end length of the uncoiled GRS according to the drug weight. **(D)** The calculated total GRS weight according to the drug weight, incorporating the weight of the polymer matrix, nitinol wire, and ends of the device.

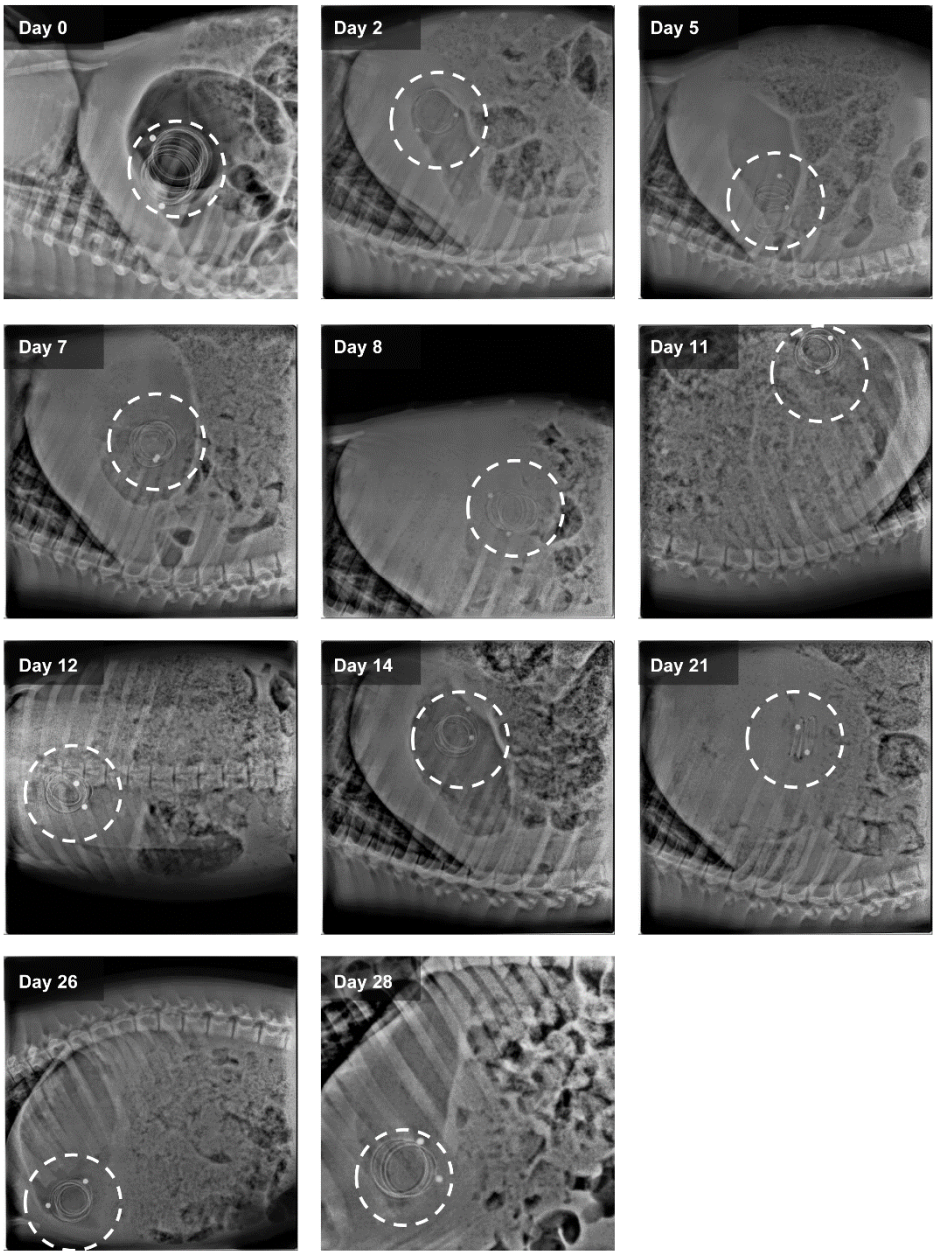



**Fig. S2. Serial radiographs of the GRS over 1 month in a swine model.** Radiographs of the gastric cavity were taken every few days over the course of 1 month to monitor for safe long-

term gastric residence of the GRS. The dotted lines encircle the GRS in the gastric cavity of the swine.

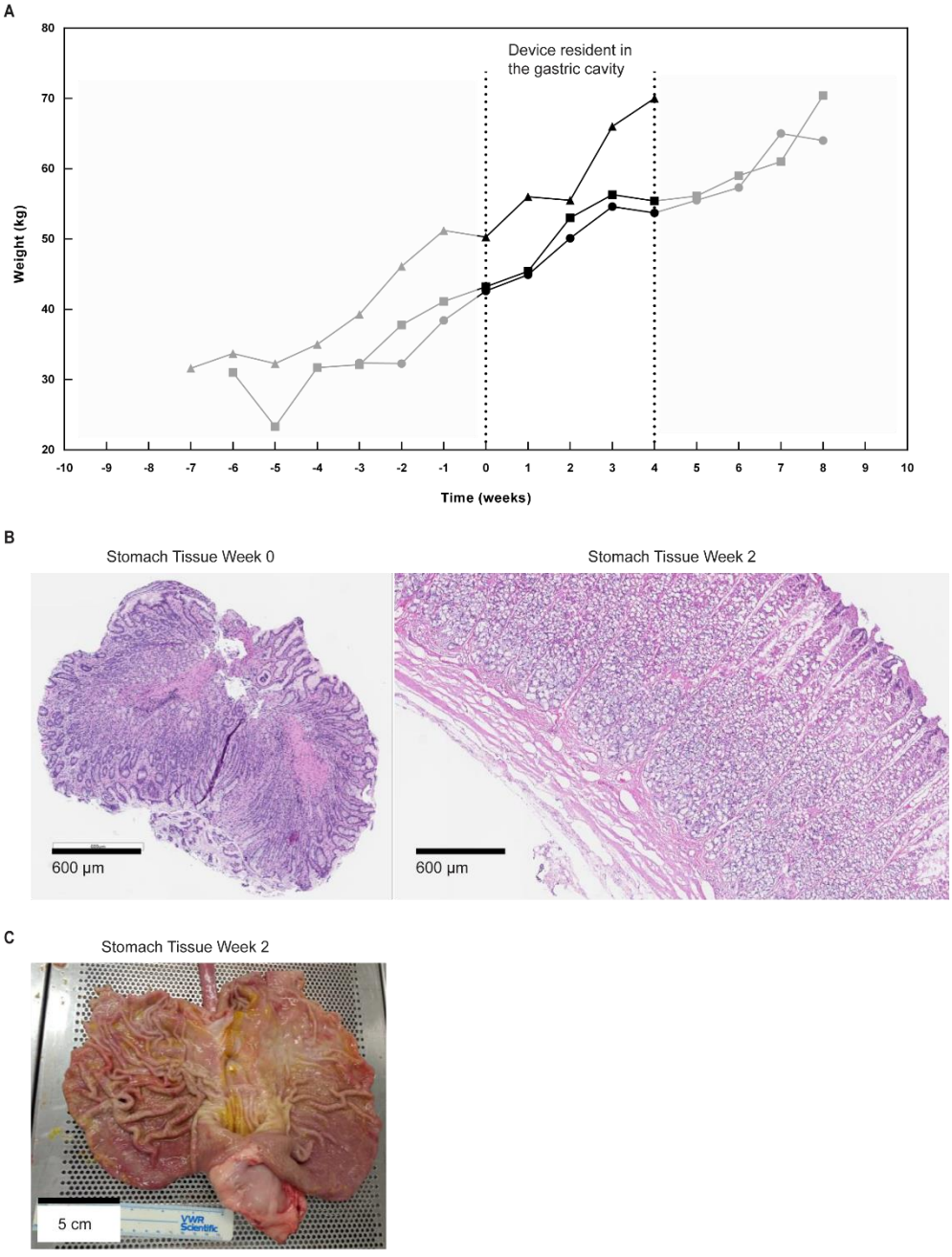



**Fig. S3. Effect of the GRS on the weight and stomach tissue of swine. (A)** The animals' weight was measured every week from when it was brought into the animal facility until when it was euthanized. Week 0 denotes the week that the GRS was administered to the gastric cavity of

the animal. At the end of week 4, the GRS was retrieved from the gastric cavity, and the animal is either euthanized immediately or is used for other studies with the weight being measured every week. **(B)** After 2 weeks of gastric residence for the GRS, the stomach mucosa was assessed for any damage. A representative hematoxylin and eosin stain of stomach tissue at week 0 (prior to deployment of the GRS) and at week 2 (when the GRS is retrieved and the animal is euthanized) is shown (n=3). **(C)** Representative macroscopic image of the stomach tissue at the end of week 2 when a GRS was retrieved from the gastric cavity and the animal is euthanized to assess any damage to the mucosa (n=3).

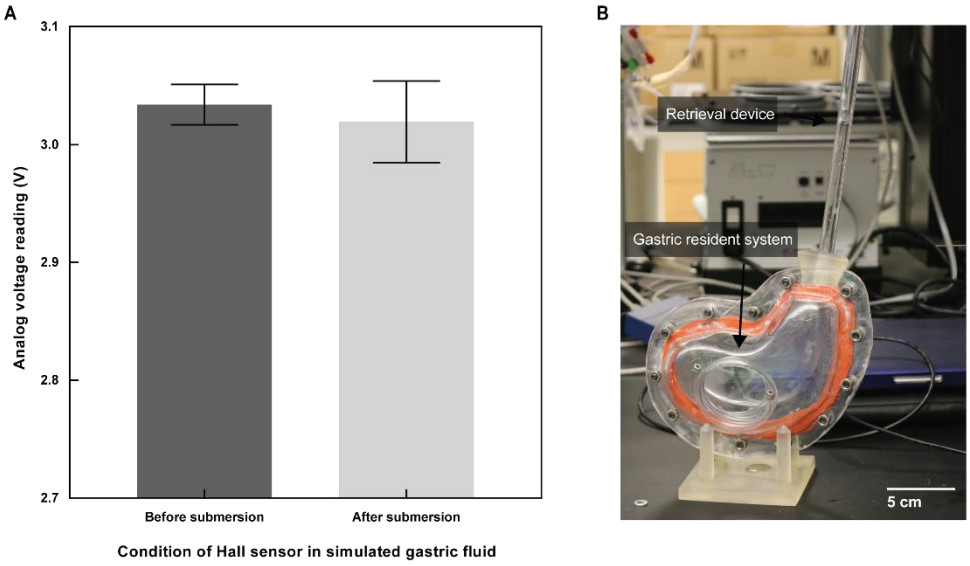



**Fig. S4. Hall effect sensor acid stability and retrieval using an in vitro stomach model. (A)** Voltage reading of the Hall effect sensor before and after submersion in simulated gastric fluid. Error bars represent the standard deviation for n = 3 samples in each group. **(B)** Photograph of a three-dimensional printed stomach model used to test sensing and magnetic attachment of the retrieval device to the gastric resident system.

A

| Formulation: Amount | Doxycyline hyclate | Silicone | PEG | Coating: Thickness |
|---|---|---|---|---|
| 1: 1 gram | 32% | 66% | 2% | Eudragit RS 100: 210 μm |
| 2: 2 grams | 32% | 68% | 0% | Eudragit RS 100: 300 μm |
| 3: 3 grams | 32% | 68% | 0% | PCL: 350 μm |
| 4: 4 grams | 32% | 68% | 0% | PCL: 650 μm |

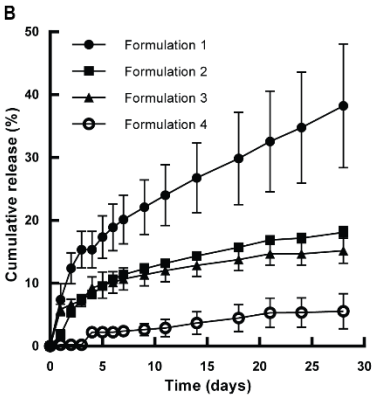



**Fig. S5. In vivo formulations and their corresponding 4-week in vitro drug release profiles of doxycycline hyclate–silicone pills of the 10 g GRS. (A)** Table of in vivo formulations for the doxycycline hyclate-silicone pills of the 10 gram GRS assembled 1 gram of formulation 1, 2 grams of formulation 2, 3 grams of formulation 3, and 4 grams of formulation 4. Formulation 1 contained poly(ethylene glycol) (PEG), whereas the others did not. All drug pills were coated with either Eudragit RS 100 (formulations 1 and 2) or with poly(Ɛ-caprolactone) (PCL) (formulations 3 and 4). **(B)** In vitro release profiles of doxycycline hyclate from drug-silicone pills over 4 weeks in simulated gastric fluid.

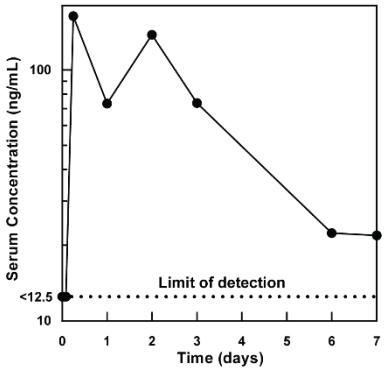



**Fig. S6. In vivo release of rifampicin from the GRS in a swine model.** A GRS with 2 grams of rifampicin formulated with 54% rifampicin and 46% silicone was administered to a swine model for 7 days, and the serum concentrations of rifampicin were recorded.

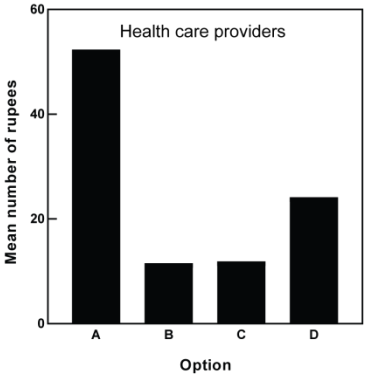
A

| Option | Description of adherence solution |
|---|---|
| A | Reduce frequency of administering medication |
| B | Send reminders to patients via cell phone or SMS |
| C | Send healthcare worker or family member to remind patient |
| D | Reward patients who take medication |

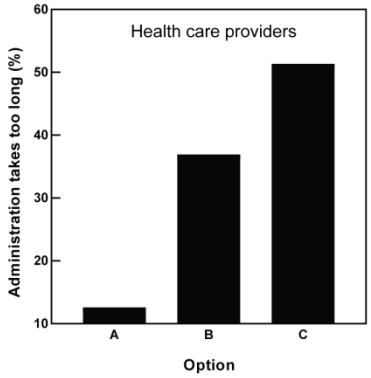
D

| Option | Route of administration |
|---|---|
| A | Nasogastric tube |
| B | Swallowing 30 “000” capsules |
| C | Drinking 2 Liters of water-drug mixture |

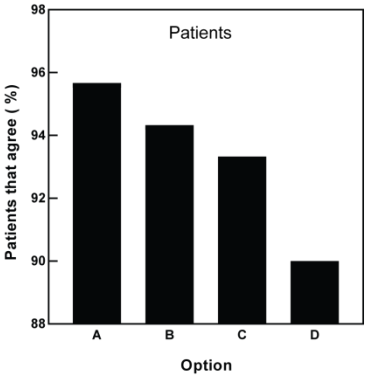
B




E




C




F

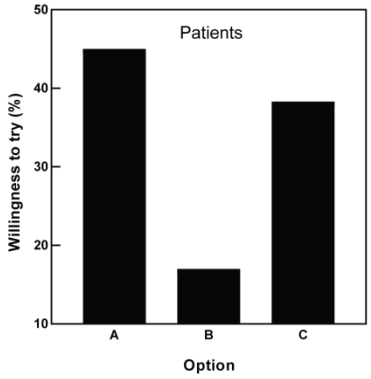


**Fig. S7. Field questionnaire results at TB clinics in New Delhi, India. (A)** Table of options presented to TB health care providers and patients with TB regarding four different methods of improving patient adherence to treatment. **(B)** Responses from health care providers on how they would allocate rupees towards four different options to improve patient adherence to treatment. **(C)** Responses from patients on whether each option would help them adhere to treatment. **(D)** Table of options presented to TB health care providers and patients with TB regarding three different routes of administering a long-term gastric resident device for TB treatment. **(E)** Responses from health care providers on the feasibility of three different routes of administration with respect to the time each option would take in a TB clinic. **(F)** Responses from patients on their willingness to try three different routes of administration for a long-lasting gastric resident device for TB treatment.

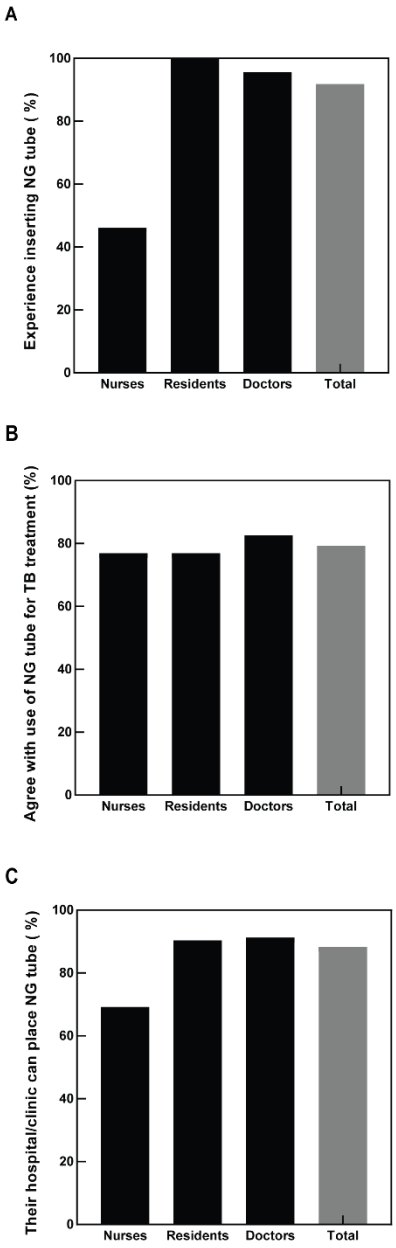



**Fig. S8. Field questionnaire results on NG tube deployment at TB clinics in New Delhi, India. (A)** Responses from all TB health care providers on their experience with inserting a NG tube previously. **(B)** Responses from all TB health care providers on whether they agree with using a NG tube for deploying TB treatment. **(C)** Responses from all TB health care providers on whether their hospital or clinic has the infrastructure to insert NG tubes in TB patients.

**Table S1. Demographics of 111 TB health care providers who responded to the questionnaire study across TB clinics in New Delhi, India.**

| Characteristics | Health care providers (N=111) n(%) |
|---|---|
| **Age (years)** | |
| 18-24 | 2 (1.8) |
| 25-34 | 64 (57.7) |
| 35-44 | 16 (14.4) |
| 45-54 | 15 (13.5) |
| 55-64 | 14 (12.6) |
| **Sex** | |
| Male | 81 (73.0) |
| Female | 30 (27.0) |
| **Occupation** | |
| Nurses | 13 (11.7) |
| Residents | 52 (46.8) |
| Doctors | 46 (41.4) |
| **TB Experience** | |
| <1 year | 12 (10.8) |
| 1-5 years | 50 (45.0) |
| 6-10 years | 16 (14.4) |
| 11-15 years | 6 (5.4) |
| >15 years | 27 (24.3) |

**Table S2. Demographics of 300 patients with TB who responded to the questionnaire study across TB clinics in New Delhi, India.**

| Characteristics | Patients (N=300) n(%) |
|---|---|
| **Age (years)** | |
| 18-24 | 54 (18.0) |
| 25-34 | 57 (19.0) |
| 35-44 | 104 (34.7) |
| 45-54 | 65 (21.7) |
| 55-64 | 14 (4.7) |
| 65+ | 1 (1.7) |
| Not sure | 5 (1.7) |
| **Sex** | |
| Male | 181 (60.3) |
| Female | 114 (38.0) |
| Other | 1 (0.3) |
| Not sure | 4 (1.3) |
| **Time at clinic** | |
| <10 minutes | 115 (38.3) |
| 10-30 minutes | 133 (44.3) |
| 30-60 minutes | 39 (13.0) |
| >60 minutes | 11 (3.7) |
| Not sure | 2 (0.7) |

**Table S3. Modeled impact of TB treatment interruptions on health and economic costs in New Delhi, India annually.**

| | |
|---|---|
| Number of patients whose treatment was interrupted | 7068 |
| Number of patients who develop MDR-TB as a result of the interruption | 707 |
| Number of patients who die as a result of the interruption | 1560 |
| Number of additional persons who develop MDR-TB as a result of the interruption | 195 |
| **Total additional cost** | |
| Provider cost | $4,631,892 |
| Household cost | $52,905,330 |
| Total | $57,537,222 |
| **Additional cost per patient** | |
| Provider cost | $655 |
| Household cost | $7,485 |
| Total | $8,141 |

**Table S4. Individual subject-level data for Fig. 2 (B to G) and 3 (C and D) figs. S3A, S4A, S5B, S6, S7 (B and C), S7 (E and F), and S8 (Excel format).**

**Data file S1. In vitro design of 3D stomach model.**

**Data file S2. Field questionnaire study to inform mode of administration.**

**Data file S3. Sensitivity analysis of health and economic model.**