

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 09: Infectious Disease Including HIV/AIDS

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,200 leads about potential topics has resulted in identification and tracking of about 1,900 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 500 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the 10 topics for which (1) preliminary phase III data on drugs, phase II or III data on devices and procedures were available, or programs were being piloted; (2) information was compiled before October 27, 2013, in this priority area; and (3) we received six to nine sets of comments from experts between April 19, 2012, and October 29, 2013. (A total of 48 topics in this priority area were being tracked in the system as of October 29, 2013.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present eight summaries of eight topics (indicated below with an asterisk) that emerged as having higher impact potential on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 09: Infectious Disease Including HIV/AIDS

Topic	High-Impact Potential
1. * Antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections	High
2. * Emtricitabine/tenofovir (Truvada) for prevention of HIV infection	High
3. * Fecal microbiota transplantation for treatment of recurrent <i>Clostridium difficile</i> infection	High
4. * OraQuick in-home rapid test for detection of HIV infection	Moderately high
5. * Retrofitted private intensive care rooms to reduce hospital-acquired infections	High
6. * RTS,S/AS01 (Mosquirix) for prevention of malaria caused by <i>Plasmodium falciparum</i>	Lower end of the high-impact-potential range
7. * Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C infection	High
8. Streaming weekly educational soap opera episodes to smartphones for people at high risk of contracting HIV infection	No high-impact potential at this time
9. * Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of <i>Mycobacterium tuberculosis</i>	Moderately high
10. xTAG gastrointestinal pathogen panel for detecting gastroenteritis	No high-impact potential at this time

Discussion

Health Care–Acquired and Bacterial Infections

Experts identified four interventions involving health care-acquired and bacterial infections as having potential for high impact: antimicrobial copper surfaces fitted to intensive care unit (ICU) equipment to reduce hospital-acquired infections, renovation of multi-patient ICUs to single-patient units to prevent health care-acquired infections, a treatment for recurrent *Clostridium difficile* infection (CDI), and a rapid test to determine whether a patient has a drug-resistant form of tuberculosis (TB).

About 2 million health care–acquired infections (HAIs) are documented in the United States annually and result in 100,000 deaths. The U.S. Centers for Disease Control and Prevention (CDC) has estimated that HAIs add \$28 billion to \$45 billion in costs to the U.S. health care system annually. On average, HAIs add an estimated 19.2 hospital days per patient contracting an HAI at a per-patient cost of \$43,000. Patients contracting an HAI have a 1-in-20 chance of dying in the hospital and a 1-in-4 chance of dying if the infection was contracted in the ICU.

Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections

- **Key Facts:** About 80% of infectious diseases are transferred by touch, according to estimates by the International Copper Association, and despite common infection-control practices (hand-washing and frequent surface disinfection) the number of HAIs each year continues to rise. Surfaces in patient rooms, including the ICU, typically consist of stainless steel and plastics that possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures.

The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment might add another safeguard against disease transmission between cleanings. Antimicrobial Copper (CuVerro® Global Brass and Copper Holdings, Inc., Schaumburg, IL) touch surfaces can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, intravenous (IV) poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties purportedly remain effective for the product's lifetime. These surfaces purportedly continuously reduce bacterial contamination and achieve a 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure. As many as 479 alloys, such as brass and bronze, have been registered to be antimicrobial, providing options to fit various clinical and aesthetic demands. Copper surfaces purportedly exert their antibacterial activity in two sequential steps: (1) by disrupting the integrity of bacterial cell membranes through oxidation and disrupting physiologic functions such as electrostatic potential and (2) by interacting with numerous enzymes crucial for normal metabolic activity through antimicrobial copper ion penetration of compromised cells to alter cell metabolism. Copper surfaces are intended to be used in combination with standard infection control procedures. Published studies have shown that antimicrobial copper surfaces have reduced the microbial burden found on surfaces in the ICU and may lead to lower infection rates in patients staying in copper-fitted rooms. In one randomized controlled trial, patients (n=650) presenting for admission to three ICUs in the United States were randomly placed in rooms fitted with six copper alloy surfaces or standard surfaces. Patients admitted to

copper-fitted rooms had a significant reduction in HAI or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci infections compared with such infection rates in patients placed in standard rooms.

In July 2012, the Agency for Healthcare Research and Quality awarded a \$2.5 million interdisciplinary research collaboration grant to the University of California, Los Angeles, to conduct a 4-year, randomized study to determine whether reducing surface bacteria through use of copper surfaces decreases HAI rates, improves treatment outcomes, and reduces costs. The study will evaluate copper, plastic, or sham stainless steel surfaces to better understand their role as fomites.

- **Key Expert Comments:** Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces could significantly reduce HAIs and associated morbidity, mortality, and costs. Although a significant capital investment may be required to retrofit frequently touched surfaces in ICUs, the intervention is expected to quickly accrue savings. Except for a one-time disruption in patient management, antimicrobial copper is not expected to alter hospital operations. Although antimicrobial copper surfaces may reduce pathogens, experts warn that infection rates may not decline as much as expected because HAIs can be contracted from bacteria already colonizing the patient's body and, thus, are not transmitted from a caregiver's hand or contaminated fomites.
- **Potential for High Impact:** High

Fecal Microbiota Transplantation for Treatment of Recurrent *Clostridium Difficile* Infection

- **Key Facts:** In 2010 in the United States, an estimated 500,000 individuals experienced CDIs at an estimated cost of at least \$1 billion. Recurrent CDI is increasingly common and challenging to treat effectively. About 15% to 30% of patients have a recurrence after treatment with metronidazole (Flagyl[®]) or vancomycin (Vancocin[®]). Vancomycin is commonly used after a second CDI recurrence, but when vancomycin therapy is stopped, up to 65% of patients develop recurrence. A relatively new antibiotic, fidaxomicin (Dificid[®]), is a third-line antibiotic therapy, but other therapeutic options are needed that do not involve antibiotic therapy.

Fecal microbiota transplantation (FMT) is a nonantibiotic option. Fecal microbiota from a healthy donor is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization. Shortly before the procedure, which can be delivered by any of several methods (e.g., capsules, colonoscopy, nasogastric tube, enema), healthy donors who have completed screening for other diseases (e.g., syphilis, HIV, hepatitis A, B, and C) submit fresh stool, which is mixed with saline into a solution and administered to the patient. Typically, this procedure is required only once in most patients to achieve a persistent resolution, although data have shown that a second administration for patients in whom CDI recurred after an initial FMT results in resolution in most of those patients. In a randomized trial of patients with recurrent CDI (n=43), 81% of patients treated with oral vancomycin followed by FMT administered through a nasoduodenal tube resolved *C. difficile*-associated diarrhea compared with 31% of patients treated with oral vancomycin alone and 23% of patients treated with vancomycin and bowel lavage (p<0.001 for both comparisons with the infusion group). Results were so compelling that the trial's Data and Safety Monitoring Board halted the trial early after an interim analysis. Researchers who analyzed data on more than 77 patients with recurrent CDI from five treatment centers across the United States who

received FMT reported that CDI was cured in 91% of patients after one treatment. Other, smaller trials have reported similar success rates, including a pilot study (n=27) in which 100% of patients were purportedly cured with oral administration of encapsulated feces. Some news reports have stated that facilities offering the procedure inform patients that a 90% success rate can be assumed.

In May 2013 at a public workshop on FMT and standards for the procedure, the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) announced that FMT falls within the agency's definition of a biological product and drug. Because CBER has not approved FMT for any therapeutic purpose, the agency has stated that it would require an investigational new drug (IND) application from any center intending to treat a patient with FMT for any condition. Several weeks later, FDA reconsidered this policy as a result of "subsequent communications, [in which] physicians and scientists have expressed concern to FDA that FMT is not appropriate for study under FDA's investigational new drug application (IND) regulations (21 CFR Part 312). Some health care providers have stated that applying IND requirements will make FMT unavailable...." FDA indicated that it "intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products." In June 2013, FDA granted Rebiotix, Inc., of Roseville, MN, fast-track designation for its proprietary off-the-shelf microbiota suspension (RBX2660) for treating recurrent CDI.

More than 700 cases treated with FMT have been reported in the literature. Additionally, some researchers are investigating the feasibility of patients banking their own fecal material upon admission to eliminate the need for donor feces. Reported costs associated with screening donor blood and stool for contagious agents, preparing the donor fecal sample, and placing a retention enema tube are estimated to be \$1,500. If the procedure is done by colonoscopy, the average cost of colonoscopy could add about \$3,710 to the total cost of the procedure (\$1,060 for patients with Medicare). However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI easily exceed the reported costs of one FMT. Third-party payers (Aetna, Humana, and HealthPartners) have started to cover the procedure for patients with CDI who do not respond to a specified number of antibiotic courses.

- **Key Expert Comments:** Overall, experts concluded that results from the small number of FMT studies completed thus far are very compelling. However, experts were eager to see larger comparative studies (comparing to antibiotic therapies) to better determine the role of FMT in clinical practice and the best processes and standards to ensure safety in screening and processing donor material. Experts noted several potential societal barriers to acceptance of the procedure and a lack of standardized protocols; however, they also noted that the severity of recurrent CDI and its impact on patient quality of life is prompting patients to seek out the procedure.
- **Potential for High Impact:** High

Retrofitted Private Intensive Care Rooms to Reduce Hospital-Acquired Infections

- **Key Facts:** Despite infection-control efforts, about one-third of patients admitted to an ICU contract an infection, which may increase length of stay, cost of care, and morbidity. HAIs can be transmitted between ICU patients by direct contact (principally via caregivers'

hands), respiratory droplets, and via fomites (medical/computer equipment, sink faucets, beds, and chairs). Although many facilities building new ICUs are building single-patient ICU rooms, most existing ICUs have multiple patient beds in one room. Renovating traditional multiple-patient ICU settings to create single-patient room designs may help to prevent and contain infections, thereby improving patient outcomes. Several design elements in private ICU rooms (i.e., increased patient area and an increased sink-per-patient ratio) can purportedly reduce HAI transmission. Additionally, single-room ICU design purportedly improves hand hygiene among health care workers. Private rooms also can help to improve patient comfort and satisfaction on HCAHPS (the Hospital Consumer Assessment of Healthcare Providers and Systems). Higher satisfaction scores could help hospitals obtain higher reimbursement and remain competitive with other hospitals. Retrofitting ICUs to a single-patient room design represents a significant investment in infrastructure and equipment, which is theorized to provide cost savings in the long term. However, investigating the effect of ICU design on HAI rates only for research purposes has been cost prohibitive. Thus, available evidence typically consists of before-and-after study design or has been gathered during outbreaks of resistant organisms during which multiple infection-control measures are used, complicating interpretation of the results.

In a prospective, parallel-assignment trial, patients in Jerusalem, Israel, treated in a unit renovated with private ICU rooms acquired fewer antibiotic-resistant infections and had more antibiotic-free days compared with both patients treated in the ICU before the renovation to private rooms and patients treated in an ICU with room dividers. Proper hand hygiene was observed more frequently for patients in private rooms than for patients treated in a unit with room dividers.

In another trial in a teaching hospital in Montreal, Quebec, Canada, ICU rooms renovated to a single-patient design reduced the acquisition of *C. difficile* by 43%, MRSA by 47%, and yeast by 51%. Patients in renovated, private ICU rooms had a 10% reduction in the adjusted length of stay compared with patients treated in rooms before the renovation.

In a retrospective study, patients (n=818) admitted to an ICU in Florence, Italy, had fewer microbiologic cultures from both bronchial aspirate and blood culture after rooms were renovated from a bay-room design to a single-patient room design. A significant decrease in antibiotic use was also observed after the renovation.

The American Institute of Architects recommended in 2006 that private rooms become the standard for new hospitals. The recommendations were developed by a panel of hospital administrators, doctors, architects, engineers, and infection-control experts. Private ICU rooms are being implemented in hospitals across the United States, particularly in newly constructed units. Building single-patient ICU rooms can cost millions of dollars; however, according to one benefit-cost analysis, the estimated net social benefit cost of a bed in a private room is about \$70,000 more than a bed in a semiprivate room. Third-party payers are not expected to provide additional reimbursement for private rooms. Additional costs for private rooms are expected to be absorbed by the facility and could potentially lead to additional out-of-pocket expense for patients.

- **Key Expert Comments:** Overall, experts concluded that results from the available studies of retrofitting ICUs with private rooms are promising. They thought that the intervention has significant potential to address the unmet need of reducing HAIs when combined with other best practices for infection control. Experts agreed that significant capital investment would be required for infrastructure and equipment for private rooms; however the experts concluded reductions in HAIs and associated liability would eventually be cost-saving.

Patients and clinicians are also expected to appreciate the improved privacy and communication provided by single-patient room designs, the experts thought.

- **Potential for High Impact:** High

Xpert MTB/RIF Test for Simultaneous Detection and Drug-Sensitivity Testing of *Mycobacterium Tuberculosis*

- **Key Facts:** According to the World Health Organization, *Mycobacterium tuberculosis* infection is highly underdiagnosed because current TB testing methods require weeks to deliver a definitive result. During that time, infected patients go untreated or may be placed on ineffective therapies, thereby continuing to spread TB and creating a significant public health hazard. Thus, the need for effective, rapid diagnostics and new treatments to address resistant strains that are emergent globally is significant. The Xpert MTB/RIF (*M. tuberculosis*/rifampicin) test (Cepheid, Sunnyvale, CA) is a nucleic acid–based test that is run on Cepheid’s GeneXpert® real-time polymerase chain reaction (PCR) system. The test is intended to simultaneously detect *M. tuberculosis* complex species and determine whether the identified bacterium is susceptible to rifampicin, a first-line therapy for TB. The assay is intended to yield results in about 2 hours, which would enable relatively rapid initiation of treatment. In July 2013, FDA granted Cepheid marketing approval for the Xpert MTB/RIF test through the de novo classification process, a regulatory pathway for medical devices considered generally of low to moderate risk but which have no comparable predicate device already approved for marketing. Xpert MTB/RIF is indicated for the rapid molecular detection of *M. tuberculosis*-complex DNA, as well as the detection of rifampin resistance associated with mutations of the *rpoB* gene in specimens positive for *M. tuberculosis*. In August 2013, FDA categorized the Xpert MTB/RIF test as “moderate complexity” under the Clinical Laboratory Improvement Amendments (CLIA), which could facilitate diffusion.
- **Key Expert Comments:** Overall, experts thought that this test has potential as a rapid, sensitive, and specific diagnostic test to address the unmet need for more rapid diagnosis and better initial management of this form of TB. This, in turn, could improve patient health outcomes and reduce disease spread, thought experts. By knowing a patient’s TB status before the patient leaves the physician’s office, appropriate treatment could be given sooner and proper infection control measures could begin to be implemented, the experts noted. The Xpert MTB/RIF test detects resistance only to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR methods of detection and provide an improved approach to diagnosis and treatment, which could improve outcomes for patients, especially those with limited access to care, and reduce disease transmission.
- **Potential for High Impact:** Moderately high

Hepatitis C Virus Infection

Hepatitis C virus (HCV) is the primary cause of death from liver disease and the leading cause for liver transplantation in the United States. According to a CDC report published in August 2012, “Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965,” an estimated 3.2 million Americans have chronic HCV infection, 75% of those infected are in this age range, and 50% to 80% of infected people are unaware they are infected. Additionally, HCV is seen in patients with HIV. Of the 1 million people with chronic HIV infection in the United States, about 50,000 also have chronic HCV infection. Some calculations

suggest that HCV-related mortality will continue to increase over the next two decades without effective new treatment. Also, total U.S. annual medical costs for HCV-infected people are expected to almost triple, from \$30 billion in 2009 to about \$85 billion by 2029. Chronic HCV infection is considered clinically “curable”—that is, the virus can be suppressed to undetectable levels with antiviral therapy. Intensive research has been ongoing, and dozens of drugs are in development in new drug classes. The relatively recent explosion in HCV drug development has come about because of effective and efficient in vitro methods that enable developers to quickly screen and evaluate potential candidates. The HCV community is particularly interested in the development of simple, all oral, interferon alfa (IFN)-free regimens with a shorter duration of therapy (8–12 weeks). Two new, oral anti-HCV drugs, simeprevir (Olysio™; Janssen Research & Development, LLC, a unit of Johnson & Johnson, New Brunswick, NJ) and sofosbuvir (Sovaldi™; Gilead Sciences, Inc., Foster City, CA), were approved by FDA November 22, 2013, and December 6, 2013, respectively, for treating chronic HCV genotype 1 in combination with IFN and ribavirin (RBV). Sofosbuvir was also approved for treating patients infected with HCV genotype 4 in combination with IFN/RBV, and as an IFN-free treatment option with RBV in patients infected with HCV genotypes 2 or 3. Sofosbuvir was also the first direct-acting antiviral agent approved for treating patients co-infected with HIV or awaiting liver transplantation. Surveys have reported that many hepatologists are purportedly “warehousing” their patients, waiting for effective, better tolerated, all-oral therapies to be available. Anecdotal evidence also exists that some clinicians would consider treating patients off-label using only the two antivirals sofosbuvir and simeprevir, basing their decision on results from a phase II trial demonstrating high sustained virologic response at 12 weeks (SVR12) in patients taking both agents together. A number of other manufacturers also have all-oral HCV regimens in phase II or phase III development. Manufacturers with the most advanced candidates include AbbVie, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, and Merck & Co., Inc. Most of these are too early in development at this time in the horizon scanning system to obtain expert opinion. However, one agent for which data were available and for which we sought expert comment emerged as having potential for high impact: sofosbuvir.

Sofosbuvir (Sovaldi) for Treatment of Chronic Hepatitis C Infection

- **Key Facts:** In May 2011, the NS3/4a protease inhibitors boceprevir and telaprevir were FDA approved for use in combination with IFN and RBV for treating chronic HCV genotype 1 infection. Protease inhibitors were shown to improve cure rates for chronic hepatitis C, genotype 1, compared with cure rates of IFN and RBV alone. However, up to half of patients with chronic HCV infection are not able to tolerate IFN-containing treatment regimens, so the search is on for an IFN-free regimen. Also, protease inhibitors have been associated with significant side effects, including anemia and severe rash, and are effective against only HCV genotype 1 infection. Thus, effective, well-tolerated, IFN-free options that are pan-genotypic are needed for chronic HCV infection.

Sofosbuvir (GS-7977; Gilead Sciences) is a uridine nucleotide analog HCV NS5B polymerase inhibitor under investigation for treating chronic HCV infection. Sofosbuvir purportedly targets the active site of the HCV RNA polymerase and inhibits elongation of the growing HCV RNA genomic transcript. Sofosbuvir is purported to have broad efficacy against multiple HCV genotypes and is being evaluated as part of multiple therapeutic regimens. In phase III clinical trials, sofosbuvir has been administered orally, once daily for 12 weeks in combination with RBV for patients infected with HCV genotype 2 or 3, and with IFN and RBV for patients infected with chronic HCV genotypes 1, 4, 5, or 6 whose disease is naïve to treatment. Sofosbuvir is also being investigated in combination with other

direct-acting antiviral agents, including a once-daily, fixed-dose combination with the NS5A inhibitor ledipasvir, as well as with the protease inhibitor simeprevir with the intention of creating a convenient all-oral treatment that would eliminate the need for IFN and/or RBV in patients with chronic HCV genotype 1 infection. In phase III clinical trials, treatment with sofosbuvir and RBV was noninferior to treatment with IFN/RBV in patients with chronic HCV genotype 2 or 3 infection who had not had earlier treatment. In patients with chronic HCV genotype 2 or 3 infection for whom IFN treatment was not an option, sofosbuvir and RBV treatment resulted in a significantly higher SVR12 rate compared with such response with placebo. Additionally, patients infected with HCV genotype 1, 4, 5, or 6 and who had no prior treatment were given sofosbuvir in combination with RBV/IFN for 12 weeks and had a significantly higher SVR12 rate than did a predefined historic control group. Sofosbuvir also achieved high SVR12 rates in patients co-infected with HIV and HCV genotype 1 after 24 weeks of therapy and genotype 2 or 3 after 12 weeks of therapy. Early data also suggest sofosbuvir could be effective in preventing HCV reinfection in liver transplant patients. In studies in which patients were given sofosbuvir and RBV, the most common side effects were dizziness, fatigue, headache, insomnia, and nausea. When patients were given sofosbuvir in combination with IFN/RBV, the most common side effects reported were anemia, fatigue, headache, insomnia, and nausea.

In April 2013, the company submitted a new drug application to FDA for sofosbuvir and RBV for treating HCV genotype 2 or 3 infection and for sofosbuvir plus IFN/RBV for patients with HCV genotype 1, 4, 5, or 6 who had had no prior treatment. In December, 2013, FDA approved sofosbuvir in combination with RBV for treating chronic HCV genotype 2 or 3 infection as well as sofosbuvir in combination with IFN/RBV for treating patients infected with chronic HCV genotype 1 or 4. Sofosbuvir was also approved for treating patients with HIV co-infection or hepatocellular whom are awaiting a liver transplant.

According to one estimate, sofosbuvir costs about \$84,000 for a 12 week treatment course. For benchmarking purposes, a standard 12-week treatment regimen of the protease inhibitor telaprevir costs about \$50,000. Boceprevir costs range from about \$26,000 to about \$48,000. Third-party payers typically cover HCV protease inhibitors as specialty tier drugs requiring prior authorization for coverage. Sofosbuvir will likely have similar coverage from third-party payers.

- **Key Expert Comments:** Overall, experts commenting on this intervention considered sofosbuvir as having high potential to address significant unmet needs for HCV treatment. Sofosbuvir, as part of an all-oral regimen, is purported to have high efficacy that is well-tolerated in patients who cannot tolerate IFN or do not want to use it. Sofosbuvir also provides a shorter and simpler dosing regimen than dosing for current treatment options. The high efficacy of sofosbuvir observed thus far in HCV genotypes other than genotype 1 is also perceived to be a significant advantage that will increase the drug's potential impact. Additional research will be needed to determine the long-term impact of sofosbuvir therapy on rates of cirrhosis, liver cancer, and liver transplantation. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.
- **Potential for High Impact:** High

HIV/AIDS

HIV infection continues to be a major public health concern, continuously challenging physicians, researchers, and public health officials to find the best practices to contain the epidemic.

HIV prevention measures remain crucial in controlling the disease. CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 61% of new infections occur in men who have sex with men (MSM) and 23% of new infections arise in women. Women are twice as likely to be infected with HIV through heterosexual contact. According to a CDC study, about half of all new HIV infections occur from the approximate 20% of persons living with HIV who are unaware of their infection. Experts identified two interventions as having potential high impact, one for preventing HIV infection and one for in-home HIV testing.

Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection

- **Key Facts:** Emtricitabine/tenofovir (Truvada®, Gilead Sciences) has gained traction as a potential option for HIV prophylaxis in men at high risk of contracting HIV and women seeking effective prevention against the viral infection. In July 2012, FDA approved emtricitabine/tenofovir once daily in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. The approval was based on data from a trial that reported that high-risk MSM who took emtricitabine/tenofovir once daily were 44% less likely to become infected with HIV-1 than MSM given placebo. However, researchers later reported that emtricitabine/tenofovir failed to protect high-risk females from contracting HIV. Experts speculated that the lack of efficacy in protecting women might be due to the drug's inability to concentrate sufficiently in vaginal tissue, which is where transmission occurs during intercourse. They also speculated lack of efficacy might be due to problems with treatment adherence, and others hypothesized that during one trial, women may have given their HIV medication to their infected partners instead of taking it themselves. These results dampened some enthusiasm and added to controversy because treatment adherence has been shown to greatly improve efficacy of prophylactic emtricitabine/tenofovir. Additionally, more recent data from two other preexposure prophylaxis studies in serodiscordant couples have shown emtricitabine/tenofovir to be 73% to 78% effective in men and women. Emtricitabine/tenofovir is also controversial because some investigators believe that the costly therapy might buy time only until infection occurs, even if the patient adheres to the recommended treatment regimen. The retail cost of a 30-day supply of emtricitabine/tenofovir is about \$1,300. Our searches found third-party payers Aetna and United Healthcare list coverage determinations specifically for preexposure prophylaxis that state both payers will cover it when the drug prescription is consistent with its indication.
- **Key Expert Comments:** Overall, experts commenting on this topic thought that prophylactic use has high potential to address an important unmet need as the first pharmacologic agent approved to reduce the risk of acquiring HIV-1 infection in patients at high risk. No other preventive options using medication are available for these individuals. However, experts noted that early trials suggest this intervention might not protect everyone who attempts the regimen. Experts speculated that this topic is controversial because of the questionable data, along with high treatment costs, a need for frequent followup for something that is not a disease (i.e., unprotected sex), and a condition that is preventable with behavior interventions.
- **Potential for High Impact:** High

OraQuick In-Home Rapid Test for Detection of HIV Infection

- **Key Facts:** Although an over-the-counter HIV test has been available since 1996, it requires that a blood sample be mailed to a laboratory for analysis; results are available the next

business day at the earliest. A simple, rapid in-home test that patients can interpret might improve HIV screening rates by increasing the privacy and confidentiality of testing. It might also empower individuals about their health decisions and provide a more rapid assessment of HIV status without the need for followup seronegative test results. Increased screening could reduce HIV transmission rates and improve disease management through earlier treatment.

The OraQuick In-Home HIV Test (OraSure Technologies, Inc., Bethlehem, PA) is a rapid, home-based HIV test that is available over the counter. OraQuick is designed to detect HIV-specific antibodies found in a patient's saliva. The test provides easy access to first-line testing that is affordable, safe, simple, rapid, painless, and anonymous. The test kit includes a single-use testing device and a test tube containing testing reagent. The testing device is a lateral flow immunoassay with an integrated oral swab. The test is predicated on an oral swab-based test that has been available to health care professionals since 2004. Changes were made only to the packaging and instructions to create the home version of the test. To conduct the test, an individual collects his or her saliva sample from along the gum line using the oral swab, then places the swab end of the testing device in the test tube with reagent for 20 minutes. The testing device contains colloidal gold particles bound to protein A, which will bind antibodies from the saliva sample in solution and migrate along the device. The tube has two indicator lines toward the distal end that are viewed by the user to determine the result—one line indicates the test result and the other that the test was valid. The kit includes resources on HIV and HIV testing, including a hotline with 24-hour customer support to answer questions regarding testing and interpretation as well as referral to care if needed. A negative test result 3 months after the last risk event is likely to be a HIV-negative result. An HIV-positive test result requires followup testing by Western blot analysis to confirm infection. In a large clinical trial (n=5,662) used to support regulatory filing, the sensitivity of this in-home HIV test was 91.67% and specificity was 99.98%.

A behavior study was conducted of a cohort of ethnically diverse MSM (n=27) who were considered at risk of contracting HIV and never or rarely used condoms, to determine whether they would use the test to screen potential sexual partners. The authors reported 10 of 100 screened individuals received a positive test result. Sixty percent of those who screened positive were unaware of their HIV status. Most study participants purportedly expressed a strong desire to continue using the home test and would buy it. The manufacturer warns that the test should not be used to make decisions on behavior that may put one at increased risk of contracting HIV.

The test became commercially available in the United States in October 2012 after its July 2012 FDA approval for sale directly to consumers. The test can detect antibodies to both HIV-1 and HIV-2. The test is the first, and so far only, rapid over-the-counter test approved by FDA for detecting HIV or any other infectious disease.

The test costs about \$40 when purchased directly from the manufacturer. Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that only Aetna lists a coverage determination for the HIV home test kit, which states the payer does not cover home HIV test kits that do not require a physician's prescription.

- **Key Expert Comments:** Overall, experts commenting on this intervention thought that the OraQuick rapid in-home HIV test has potential to meet a significant unmet need by

increasing HIV screening rates in patients who engage in high-risk behaviors but are reluctant to undergo HIV screening in clinics. In-home testing was thought to have potential to improve screening rates because of its relatively modest \$40 cost to purchase and perform testing. Experts commented that patients who know their HIV status are more likely to seek treatment and avoid high-risk behaviors, which could positively affect public health outcomes and reduce costs to the system. However, for patients with positive results, more patients would likely seek treatment, thereby increasing care costs to the health system. Experts theorized OraQuick's use could also affect patient management when patients with a positive home test present at health clinics for additional testing. They may have a high level of anxiety from a lack of pretest counseling. Experts believe that the test has the potential to reduce the number of "worried well" patients that clinicians encounter for testing.

- **Potential for High Impact:** Moderately high

Malaria

Globally, an estimated 219 million people were infected with malaria and 660,000 people died from the disease in 2010, despite disseminated use of vector control with insecticide-treated bed nets and indoor residual spraying combined with intermittent prophylactic pharmacotherapy. Malaria places a significant economic burden on developing nations, accounting for an estimated 40% of medical costs, 60% of visits to health clinics, and up to half of all hospitalizations in endemic countries. Malaria is the second leading cause of death in Africa and the leading cause of death in Africa in children younger than 5 years of age. People traveling to endemic areas (e.g., vacation, expatriation, military service) are also at risk of contact with infected mosquitoes. Although malaria has largely been eliminated from the United States, about 1,500 cases are reported annually. Between 1957 and 2011, 63 outbreaks of locally transmitted malaria were documented. The outbreaks occurred from local mosquitoes that were infected from biting people carrying malaria parasites that were acquired in endemic areas. The infected mosquitoes then transmitted malaria to local residents; thus, the potential risk of reemergence still exists. Children, pregnant women, the elderly, and immunosuppressed individuals have the highest risk of mortality. Vaccination against malaria parasites such as *Plasmodium falciparum*, the most deadly species of malaria parasite, could reduce the incidence of malarial disease in people living in or traveling to endemic areas. One intervention for preventing malaria was identified for this report as having high-impact potential.

RTS,S/AS01 (Mosquirix) for Prevention of Malaria Caused by *Plasmodium Falciparum*

- **Key Facts:** Malaria represents a significant burden to the health care systems of countries endemic for the disease as well as a significant health concern for people planning to travel to endemic areas. No licensed vaccines exist for preventing malarial disease; current prevention methods include vector control in the form of insecticide-treated bed nets, residual spraying, and personal mosquito repellent, as well as prophylactic use of antimalarial drugs. RTS,S/AS01 is a prophylactic vaccine in clinical development designed to prevent malarial disease caused by the parasite *P. falciparum*. RTS,S/AS01 is a recombinant protein consisting of the central repeat and C terminal portions of the *P. falciparum* circumsporozoite protein fused to hepatitis B virus surface antigen, expressed in *Saccharomyces cerevisiae* with excess hepatitis B virus surface antigen to facilitate the formation of virus-like particles. RTS,S/AS01 also contains the novel proprietary AS01

adjuvant. The vaccine is purported to be a “pre-erythrocytic vaccine” that induces protective antibody responses that prevent sporozoites from invading hepatocytes during the short window of time in which sporozoites are in circulation or by attacking liver schizonts. RTS,S/AS01 is also purportedly induces strong interferon gamma-producing CD4+ T-cell responses, which could contribute to killing liver schizonts.

In a phase III randomized trial, children (n=6,537) aged 6–12 weeks vaccinated with RTS,S/AS01 had a 31.3% reduction in the first or only episode of clinical malaria up to 14 months after the first dose of vaccine compared with that outcome in children given a control vaccine in the per-protocol population. Children given RTS,S/AS01 had a 36.6% reduction in severe malaria in the per-protocol population. In a phase III randomized trial, children (n=6,000) aged 5–15 months or aged 6–12 weeks were given RTS,S/AS01 or a nonmalaria control vaccine. RTS,S/AS01 was 55.8% effective against clinical malaria in the 14 months after the first dose of vaccine in children aged 5–15 months in the per-protocol population. The vaccine was 47.3% effective against severe malaria in children aged 5–15 months in the per-protocol population. Children given RTS,S/AS01 had no differences in the frequency of serious adverse events compared with children given control vaccine. Patients aged 5–15 months who were given RTS,S/AS01 reported generalized convulsive seizures at a rate of 1.04 per 1,000 doses.

Some investigators theorize that RTS,S/AS01 may reduce the risk of infection from each malaria exposure, rather than conferring “all or nothing” protection to those taking the vaccine; thus, vaccinated individuals could eventually experience malaria if the transmission rate is high enough. The vaccine is expected by investigators to have a greater impact on the incidence of the first or total episodes of clinical malaria instead of on the overall population experiencing disease.

- **Key Expert Comments:** Overall, experts stated the high burden of disease and suboptimal methods of malaria prevention present a significant unmet need for new interventions to prevent malarial disease for people living in or traveling to areas endemic for *P. falciparum*. The experts stated that the efficacy seen in children aged 6–12 weeks and children aged 5–17 months could provide a significant improvement in health outcomes. However, the experts noted that suboptimal efficacy and waning protection provide a need for further development of second-generation vaccines. RTS,S/AS01 is expected to reduce demands on malaria treatment facilities in endemic areas, but could require additional infrastructure investment for cold chain management (controlling the temperature at which the vaccine is shipped and stored) and patient followup for subsequent booster immunizations.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Health Care-Acquired and Bacterial Infection Interventions

Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections

Unmet need: Health care-associated infections (HAIs) are a significant cause of mortality, morbidity, and costs in the U.S. health care system.¹ About 80% of infectious diseases are transferred by touch, according to estimates by the International Copper Association.² About 2 million HAIs are documented in the United States annually and result in 100,000 deaths.³ Additionally, the U.S. Centers for Disease Control and Prevention (CDC) estimates that HAIs add between \$28 billion and \$45 billion to annual U.S. health care costs.⁴ On average, HAIs add an estimated 19.2 hospital days and \$43,000 in additional costs for each patient who contracts an HAI.⁵ Further, patients contracting an HAI have a 1-in-20 chance of dying if the infection is acquired while hospitalized and a 1-in-4 chance of mortality if the infection is contracted in the intensive care unit (ICU).⁶

Hospital surfaces in patient rooms, including the ICU, typically consist of stainless steel and plastics that purportedly possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures in many health care settings. In some cases, these surfaces can be colonized with live microbes for days or weeks, providing a contamination source to the hands and equipment of health care workers, professionals, visitors, and patients. The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment could add another safeguard against disease transmission between cleanings.⁷

Intervention: Antimicrobial copper touch surfaces (CuVerro[®] Global Brass and Copper Holdings, Inc., Schaumburg, IL) can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, intravenous (IV) poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties purportedly remain effective for the product's lifetime, and they do not rely on coatings or impregnated surfaces that may wear off or wash away.⁷ The manufacturer association claims that copper touch surfaces continuously reduce bacterial contamination, achieving 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure and that the surface delivers continuous antibacterial activity between routine cleaning and sanitizing steps.^{8,9}

Antimicrobial copper consists of copper alloys such as brass and bronze, copper nickels, and copper with nickel and zinc.^{1,10} Manufacturers intend these alloys to have strength comparable to stainless steel. Copper alloys are purported to be durable. Natural tarnishing does not impair the surface's efficacy, and copper touch surfaces have been deemed to not be harmful to people or the environment.^{1,11}

The manufacturer purports that copper surfaces exert their antibacterial activity in two sequential steps. First, antimicrobial copper purportedly disrupts the integrity of bacterial cell membranes through oxidation and disrupts physiologic functions such as electrostatic potential. Second, copper ions purportedly penetrate compromised cells and alter cell metabolism by interacting with numerous enzymes crucial for normal metabolic activity.¹² The use of antimicrobial copper is intended to supplement and not substitute for standard infection control practices, and users are advised to continue to follow all current infection control practices.⁸

Antimicrobial copper is commercially available in certain hospital settings, such as on door knobs and door push plates. Thirteen companies are positioning to manufacture products containing the Antimicrobial Copper mark.¹³

Clinical trials: In a randomized controlled trial, patients (n=650) admitted to three ICUs in the United States were randomly placed in rooms fitted with six copper alloy surfaces (bed rails, overbed tables, IV poles, arms of the visitor's chair, and any two of the following items: nurses' call button, computer mouse, bezel of the touchscreen monitor, or palm rest of a laptop computer) or standard surfaces.¹⁴ Patients admitted to copper rooms had a 45% reduction in HAI or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) compared with those infection rates in patients placed in standard rooms (p=0.020).¹⁴ Additionally, patients assigned to rooms with copper surfaces had a 58% reduction in contracting an HAI alone compared with HAIs in patients placed in standard rooms (p=0.013).¹⁴

In another analysis, investigators sampled copper-containing objects (n=282) in 32 ICU rooms and noncopper-containing objects (n=288) in 27 ICU rooms to examine the ability of antimicrobial copper to lower the microbial burden (MRSA and VRE) on commonly touched objects and to mitigate the acquisition of HAIs. The copper content of the objects was as follows:

- Bed rails, 99.99% copper alloy
- Tray tables, 90% copper alloy
- Chair arms, 90% copper alloy
- Monitors, 90% copper alloy
- IV poles 75% to 95% copper alloy
- Call buttons, 70% to 95% copper alloy

Using copper significantly reduced the total mean microbial burden in the ICU room by 87.4% (p=0.003). Copper was also effective in reducing the mean microbial burden on four of the six objects (bedrails [reduced by 99%, p=0.0003], call buttons [by 90%, p=0.003], IV poles [by 67%, p=0.11], and chair arms [by 38%, p=0.11]). Using copper showed no reduction in the mean microbial burden on tray tables or monitors.

Staphylococcus was the predominant organism isolated from each object regardless of the surface composition and comprised 78.7% of the mean microbial burden of copper-containing rooms and 55.5% of rooms that were not copperized. According to investigators, MRSA and VRE were frequently isolated from noncopper-containing objects but were not isolated from copper-containing objects.¹⁵

Manufacturer and regulatory status: The International Copper Association, Ltd., New York, NY, advocates for Antimicrobial Copper. It is the only hospital touch surface with a U.S. Environmental Protection Agency (EPA) public health registration, allowing manufacturers to claim that copper surfaces can kill specific bacteria (*S. aureus*, MRSA, VRE, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli* O157:H7) that cause infections and pose a threat to human health.⁸ Although the manufacturer association makes no claims of efficacy against other organisms, the literature has shown that the copper might also be effective against viruses, other bacteria, and fungal pathogens.^{7,16} More than 479 antimicrobial copper alloys are EPA-registered public health antimicrobial products available to address both practical and aesthetic demands.¹⁷

Diffusion: The additional cost of manufacturing a copper sink for a hospital room is estimated at \$40–\$60 each, which might be considered marginal considering the cost for a hospital sink of approximately \$7,500.¹⁸ Additionally, copper rails are expected to add approximately \$100 to the cost of a standard \$30,000 hospital bed.¹⁸ According to the Copper Development Association, equipping each U.S. hospital room with antimicrobial copper products could cost from \$1.5 billion to \$2.5 billion, and a return on investment might be realized within 1.0–1.5 years after implementation.¹⁸

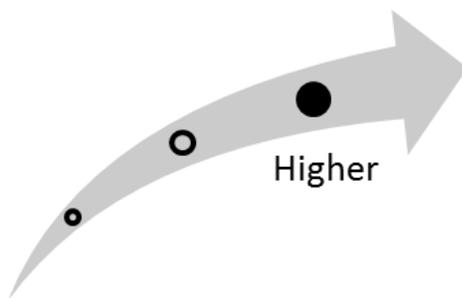
In July 2012, a research collaboration involving teams from the David Geffen School of Medicine at University of California, Los Angeles (UCLA), the UCLA Fielding School of Public

Health, and the Henry Samueli School of Engineering and Applied Science at UCLA announced that the U.S. Agency for Healthcare Research and Quality (Rockville, MD) had awarded them \$2.5 million to conduct a 4-year, randomized study to determine whether reductions of surface bacteria due to the use of copper surfaces lead to decreased HAI rates, improve treatment outcomes, and reduce costs. The study will evaluate copper, plastic, or sham stainless steel surfaces to determine their role in HAI transmission.¹⁹

Clinical Pathway at Point of This Intervention

ICUs typically contain stainless steel and plastic surfaces that are disinfected with standardized terminal cleaning procedures when patients are discharged from a room. Antimicrobial copper touch surfaces might help prevent the accumulation of pathogens between cleanings.²⁰

Figure 1. Overall high-impact potential: antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections



Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces might significantly reduce HAIs and associated morbidity, mortality, and costs. Although a significant capital investment may be required to retrofit frequently touched surfaces in ICUs, the intervention is expected to quickly provide durable cost savings and improved patient outcomes. Except for a one-time disruption in patient management, using antimicrobial copper is not expected to alter hospital operations. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.²¹⁻²⁷ We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Overall, the unmet need of reducing HAIs is quite significant, the experts agreed, noting current infection-control practices and education have not lowered these rates adequately in many cases. Also, new Medicare rules declining to reimburse for hospital readmissions arising from a HAIs have contributed to the unmet need. Overall, these experts stated that copper surfaces might help address the unmet need by reducing HAIs.

Acceptance and adoption: The practice of using antimicrobial copper surfaces in ICUs would be widely accepted by both patients and physicians, the experts thought. They indicated this intervention might be a simple, nontoxic way help to solve a complex and burdensome problem in health care. Experts stated that patients will likely accept an intervention that is expected to improve their health outcomes. One expert representing a clinical perspective stated that physicians are more likely to accept this intervention if they will not personally bear the cost of fitting facilities with antimicrobial copper. This idea was fleshed out by another expert, representing a health systems

perspective, who stated that acceptance by clinicians or patients will be secondary to acceptance by health systems administrators, whose acceptance will be crucial to implement the intervention. The experts also stated that although a one-time capital investment for new copper fixtures (which are slightly more expensive than current fixtures) is required, they are likely to be cost-saving within a year or two because extended ICU admissions can be among the most expensive occurrences in health care.

Health care delivery infrastructure and patient management: A one-time disruption in infrastructure and patient management would result from implementing copper touch surfaces in ICUs, the experts stated, noting that rooms would be unavailable during retrofitting with copper surfaces. Implementing copper surfaces into new infrastructure and equipment purchased is expected to be easier than retrofitting existing surfaces.

Fecal Microbiota Transplantation for Treatment of Recurrent *Clostridium Difficile* Infection

Unmet need: In 2010 in the United States, an estimated 500,000 individuals were infected with *Clostridium difficile* infections (CDIs) at a cost of at least \$1 billion.²⁸ Inappropriate antibiotic use can disturb the normal bacterial flora of the colon, leading to colonization with *C. difficile* and release of toxins that cause mucosal inflammation and damage. Patients infected with *C. difficile* typically have watery diarrhea, fever, appetite loss, nausea, and abdominal pain or tenderness.²⁹ Chronic and relapsing CDIs are increasingly common and a challenge to treat; about 15% to 30% of patients have a recurrence after treatment with metronidazole (Flagyl[®]) or vancomycin (Vancocin[®]).²⁸ Vancomycin is commonly used after a second CDI recurrence. Up to 65% of these patients develop further recurrence after antibiotic therapy is stopped. Fidaxomicin (Dificid) is a relatively new antibiotic for third-line treatment, but nonantibiotic therapeutic options are needed.²⁸

Intervention: Fecal microbiota transplantation (FMT) from the stool of a healthy donor is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization.³⁰ The treatment can be delivered by any of several methods—capsules, colonoscopy, nasogastric tube, or enema.^{31,32} Method standardization is lacking at this time. For the colonoscopic FMT procedure, healthy donors submit fresh stool on the day of the procedure, and it is mixed with saline into a solution and tested for pathogens, including syphilis, HIV, and hepatitis A, B, and C (the exact pathogens depend on the center). Prospective donors are excluded if they recently used antibiotics or had a bout of diarrhea. The fecal-saline solution is introduced into the patient's right cecum in the intestine by a gastroenterologist, who uses a colonoscope. The remainder of the solution is introduced distally as the colonoscope is withdrawn. Approximately 300–500 mL is infused into the patient; the dose varies by patient weight. For the encapsulated procedure, fecal solution is centrifuged and the fecal pellet is divided by aliquot into 24–34 gelatin pellets, which are ingested over 5–15 minutes on an empty stomach.³² Typically, FMT is required only once in a patient, although it can be repeated if the infection does not fully resolve.^{28,33}

Clinical trials: In an open-label, randomized controlled trial, patients (n=43) were randomly assigned to receive vancomycin (500 mg orally, 4 times daily, for 4 days) followed by bowel lavage and subsequent FMT administered through a nasoduodenal tube; standard vancomycin (500 mg orally, 4 times daily, for 14 days); or standard vancomycin with bowel lavage. The primary endpoint was resolution of diarrhea associated with CDI without relapse after 10 weeks. Among FMT-treated patients, 81% had resolution after the first infusion. Two of three patients whose CDI had not resolved after the first infusion had resolution after a second infusion from a different donor. CDI resolution occurred in 31% of patients treated with vancomycin alone and in 23% of patients given vancomycin and bowel lavage (p<0.001 for both comparisons with the FMT group). The reported adverse events among the three groups were few and similar, except for mild diarrhea and abdominal cramping in the FMT infusion group on infusion day. The Data and Safety Monitoring Board halted the study early after an interim analysis because of the high efficacy of FMT.³⁴

In an analysis from five treatment centers across the United States, FMT was reported to be 91% effective in patients (n=77) with recurrent CDI. The mean age of the patient population was 65 years, and 40% of these patients were hospitalized, homebound, or in a specialized nursing facility at the time of the procedure. The median time of illness before therapy was 11 months, and the mean number of courses of antibiotic therapy was five before treatment. Patients given FMT had a mean time to resolution of diarrhea of 6 days. During long-term followup, only patients who were

treated later with antibiotics (n=7) had a CDI recurrence. Two of these patients were successfully re-treated with FMT after an unsuccessful course of vancomycin. Also, 53% of patients in this study stated they would have preferred FMT as first-line treatment.³⁵

In another trial, patients (n=70) with recurrent CDI were treated with colonoscopic FMT. All patients had CDI diarrhea resolution except those infected with strain type 027 CDI, and they had an 89% response rate. Four patients who did not respond to FMT had preexisting serious conditions caused by chronic diarrhea or a comorbidity, and all subsequently died of colitis. Within the first year after FMT, four patients previously treated had a CDI relapse after being treated with antibiotics. Two of these patients were successfully re-treated with FMT, and two were treated with antibiotics for CDI.³⁶

In another retrospective study, patients (n=49) with either moderate and recurrent or severe refractory CDI were treated with FMT via nasogastric tube (74%) or colonoscopy (26%).³⁷ Ninety-four percent of patients exhibited resolved symptoms within 1–4 days. Three patients whose symptoms did not respond to therapy were concurrently taking antibiotics. Four patients had recurrence after FMT and eventually died; however, the deaths were not attributed to recurrent CDI. No adverse events were reported in patients who underwent FMT.³⁷

In another trial, prospective data were collected from three different centers performing FMT on 37 patients with recurrent CDI.³⁸ Patients received one or two FMTs. Ninety-two percent of patients were cured (range at the three centers, 75% to 100%). Two experienced a recurrence 5–12 months after receiving subsequent antibiotic treatment and were successfully re-treated with FMT. One patient who was not cured died of toxic megacolon after 1 month. He had refused the suggested operative treatment before the FMT.³⁸

In another prospective study, patients (n=27) with more than 3 recurrences of CDI were treated with FMT from related donors administered orally, via 24–34 gelatin capsules ingested orally.³² All of the patients were successfully treated up to 6 months after the procedure.³²

Manufacturer and regulatory status: Until early 2013, FMT was being carried out without regulatory oversight in the United States. Clinician concerns and the lack of clear regulatory guidance for donor screening and donor material processing for FMT led a few specialty societies including the American Gastroenterological Association to contact the U.S. Food and Drug Administration (FDA) in April to clarify whether FMT was subject to regulation.³⁹ FDA's Center for Biologics Evaluation and Research determined that FMT falls within the agency's definition of a biological product and a drug.⁴⁰ The agency held a public workshop on FMT in May 2013 to exchange information and experience with the scientific and medical communities and to facilitate clinical development of the procedure.⁴⁰ FDA initially announced that use of FMT would require an investigational new drug (IND) application to carry out the procedure for any condition.⁴⁰ In clinical situations in which FMT may require urgent action, clinicians were instructed to contact FDA to obtain an "emergency use" IND.³⁹ Several weeks later, FDA reconsidered this policy as a result of "subsequent communications, [in which] physicians and scientists have expressed concern to FDA that FMT is not appropriate for study under FDA's investigational new drug application (IND) regulations (21 CFR Part 312). Some health care providers have stated that applying IND requirements will make FMT unavailable...."⁴¹ FDA noted the concerns and indicated that it "intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks."⁴¹

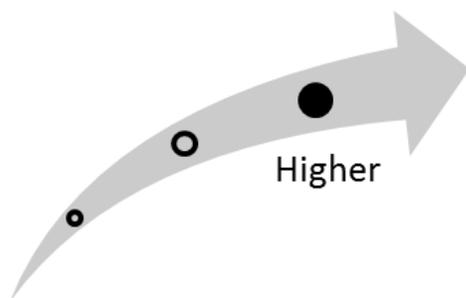
In June 2013, FDA granted fast-track designation for RBX2660 (Rebiotix, Inc., Roseville, MN) a proprietary microbiota suspension intended for standardized off-the-shelf use for treating recurrent CDI.⁴² Additionally, some researchers are investigating the feasibility of patients banking their own fecal material upon admission to eliminate the need for identifying and screening donors.⁴³

Diffusion: The procedure had been diffusing before the FDA action in early 2013. According to one estimate, more than 700 cases of FMT have been reported in the literature.⁴⁴ Diffusion could be slowed somewhat because the procedure now can be performed legally only within the context of an FDA-approved IND trial or with an emergency IND. Reported costs associated with screening donor blood and stool for contagious agents, preparing the donor fecal sample, and placing a retention enema tube are estimated to be about \$1,500.^{45,46} If the procedure is done by colonoscopy, the average cost of colonoscopy could add about \$3,710 to the total cost of the procedure (\$1,060 for patients with Medicare).⁴⁶ However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI can easily exceed the reported costs of one FMT.⁴⁶ According to one analysis, FMT by colonoscopy is more cost effective than metronidazole, vancomycin, or fidaxomicin therapy for treating the first episode of CDI, and it is more cost effective than administering FMT by enema or nasogastric tube due to improved outcomes.⁴⁷ Third-party payers (e.g., Aetna, Humana, HealthPartners) are starting to cover the procedure for patients with CDI whose condition has not responded to a specified number of antibiotic courses.⁴⁸⁻⁵⁰

Clinical Pathway at Point of This Intervention

According to CDC, once CDI is confirmed, patients should be taken off the antibiotic that created the environment for the infection to occur. In some patients (20%, within 2–3 days) the infection may resolve without further treatment. If it does not, the patient is typically treated with either oral metronidazole or vancomycin for 10 days.⁵¹ FMT is intended to treat recurrent CDI, although it is also under study as first-line therapy.

Figure 2. Overall high-impact potential: fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection



The expert comments we received predated the recent FDA action regarding regulation of FMT. Overall, experts concluded that results from FMT studies completed thus far are very promising. They thought that the procedure has significant potential to address the unmet need for effective treatment for CDI recurrence by providing a relatively low-cost, effective treatment, preventing antibacterial resistance, reducing the probability of CDI transmission, and lowering CDI-associated mortality. However, experts were eager to see larger studies to better determine the role of FMT in clinical practice and whether it should be first-line therapy for CDI. Experts noted that several societal barriers to acceptance of the procedure may slow diffusion; however, they also noted that hesitation on the part of patients might be mitigated by poor quality of life and ongoing illness in

patients with recurrent CDI. Experts stated that clinicians will have greater acceptance of the procedure once donor screening, testing, and transplant-processing protocols are established. Experts thought that FMT has high potential to significantly improve health outcomes in patients with difficult-to-treat, recurrent CDI. As the potential role of this intervention continues to be defined by clinicians using it, the procedure's unconventional and controversial nature could continue to provide catchy headlines for the media, they opined. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.⁵²⁻⁵⁸ We have organized the following discussion of expert comments by the parameters on which experts commented. Please note that the expert comments received predated the very recent FDA action regarding FMT regulation.

Unmet need and health outcomes: Recurrent CDI causes great morbidity, mortality, and costs to patients and the health care system, the experts concurred, and emerging antibacterial resistance associated with these infections represents an important unmet need. FMT has the potential to address the unmet need for recurrent-CDI treatment that does not use antibiotics, according to a general consensus among the experts; meeting this need could significantly affect health outcomes and quality of life. In general, the experts accepted the underlying theory of FMT and were somewhat certain that it could be highly effective, although they thought larger trials are needed to bear this out.

Acceptance and adoption: Clinicians would increasingly accept the procedure as donor selection, screening, and transplant processing protocols become standardized, the experts thought. Patients with long-term CDI recurrence, as well as their treating physicians, might be eager to try any therapy that has a high likelihood of efficacy. However, psychological factors or religious beliefs may preclude some patients from seeking the treatment. One expert representing a clinical perspective thought that to increase acceptance, the procedure might need to be given a different name.

Experts generally viewed the procedure as cost neutral or cost saving compared with the cost of multiple failed courses of antibiotics and resultant complications.

Health care delivery infrastructure and patient management: The experts mentioned that health care facilities generally have the staffing and equipment needed to perform the procedure, and they thought minimal disruptions would be seen in infrastructure and patient management. Potential disruptions cited would include shortened duration of inpatient stays, reduction in ICU admissions for toxic megacolon, and transition from inpatient to outpatient treatment with FMT.

Retrofitted Private Intensive Care Rooms to Reduce Hospital-Acquired Infections

Unmet need: Despite infection-control efforts, about one-third of patients admitted to an ICU contract an infection, which may increase length of stay, cost of care, and morbidity. HAIs can be transmitted between ICU patients by direct contact (principally via caregivers' hands), droplets (from infected airway secretions), and via fomites (inanimate shared objects in patient rooms or ICU environment, including computer equipment, sink faucets, beds, and chairs).⁵⁹ Private ICU rooms may help to better isolate patients and contain their infections or prevent them from contracting a new infection, improving patient outcomes.⁶⁰ Newly constructed ICUs are often built with private rooms, but the majority of existing ICUs have multiple-patient rooms and may pose increased risk of HAI to patients.

Intervention: Converting traditional multiple-patient ICU settings to a single-patient room design might reduce HAI transmission to patients who already have serious infirmities. Several design elements in private ICU rooms can purportedly reduce HAI transmission; however, the contribution of each element remains unclear.⁵⁹ Increased patient area and an increased sink-per-patient ratio are among the elements thought to reduce HAI transmission. Additionally, some investigators theorize that single-room ICU design improves hand hygiene adherence among health care workers.^{59,61} Separating patients as well as their equipment is thought to provide additional benefit; thus, single room designs within an open plan could be inadequate because the environment around the single room could provide a reservoir for HAI transmission.⁵⁹

Besides HAI-reduction association, private rooms are more accommodating for family members staying with patients in the ICU, which could decrease the patient's stress and improve privacy.⁶² Private rooms are considered the standard for new construction as hospitals position themselves to score high on the government-developed patient satisfaction rating system, HCAHPS (the Hospital Consumer Assessment of Healthcare Providers and Systems) and to remain competitive with other treatment facilities.⁶²

Although private ICU rooms represent a significant investment in infrastructure and equipment, they are purported to be part of the greater environment of healing, which can provide cost savings in the long term.⁶² However, investigating the effect of ICU design on HAI rates only for research purposes has been cost prohibitive. Thus, available evidence typically consists of a before-and-after study design or has been gathered during outbreaks of resistant organisms during which multiple infection-control measures are implemented, complicating analysis.⁵⁹

Clinical trials: In a prospective, parallel-assignment trial, patients in Jerusalem, Israel, were treated in ICUs with either seven open-plan beds (ICU-A) or four beds with dividers (ICU-B). In March 2007, patients in ICU-A were moved to a new location consisting of eight beds each in a private room, while patient-treatment spaces ICU-B were unchanged. Following the move to private rooms the following occurred:⁵⁹

- ICU-A patients acquired fewer antibiotic resistant organisms (3/62, 5%) than patients who remained in ICU-B with room dividers (7/39, 18%; $p=0.043$, $p=0.011$ using survival analysis)
- ICU-A patients after the move acquired fewer antibiotic resistant organisms than patients in ICU-A before moving to private rooms (14/62, 23%; $p=0.004$, $p=0.012$ on survival analysis)
- Patients in ICU-A had more antibiotic-free days after moving to private ICU rooms (median=3, interquartile range=0–5) than patients who remained in ICU-B with room

dividers (median=0, interquartile range=0 to 4; p=0.070) or patients in the ICU-A group before moving to private rooms (median=0, interquartile range=0 to 4; p=0.017)

Additionally, proper hand hygiene was observed on 58% of occasions after patients in ICU-A were moved to private rooms compared with 35% of occasions for patients who remained in ICU-B with room dividers (p<0.001).⁵⁹

In another trial, patients in a teaching hospital in Montreal, Quebec, Canada, were admitted to an ICU with multiple-bed rooms before a renovation (2,732 admissions) or single-patient ICU rooms after a renovation (5,468 admissions). As a control, new infection rates were collected from patients in an ICU at a nearby teaching hospital with both room designs during the study period. Statistical modeling was used to adjust for background time trends common to both hospitals. Renovating ICU rooms to single patient design reduced the adjusted combined rate of *C. difficile*, vancomycin-resistant Enterococcus species, and MRSA acquisition by 54% (95% confidence interval [CI], 29% to 70%). Single-room renovations reduced the rates of organism acquisition as follows:⁶³

- *C. difficile*, reduced by 43% (95% CI, 7% to 65%)
- MRSA, reduced by 47% (95% CI, 1% to 71%)
- Yeast, reduced by 51% (95% CI, 34% to 64%)

Patients in renovated, private ICU rooms had a 10% (95% CI, 0% to 19%) reduction in the adjusted length of stay compared with patients treated before the intervention.⁶³

In a retrospective study of HAI acquisition, results from patients (n=818) admitted to an ICU in Florence, Italy, were analyzed. From April 2006 to April 2007, admitted patients were treated in rooms with a bay-room ICU design. From May 2007 to May 2008, patients were treated in a renovated ICU with a single-room design.⁶⁴ Reductions in microbiological cultures from both bronchial aspirate and blood culture were observed after rooms were renovated to a single-room design. Respiratory isolates of *E. coli*, *Enterobacter spp*, MRSA, *Proteus mirabilis*, and *Serratia marcescens* were significantly reduced.⁶⁴ Renovation to a single-room design also reduced gram-negative bloodstream infections. A significant decrease in antibiotic use, including amoxicillin/clavulanate (p<0.01), ceftriaxone (p<0.01), oxacillin (p<0.05), and vancomycin (p<0.05), was observed after single-room renovation.⁶⁴

Manufacturer and regulatory status: The American Institute of Architects recommended in 2006 that private rooms become the standard for new hospitals. The recommendations were developed by a panel of hospital administrators, doctors, architects, engineers, and infection-control experts.⁶² Private ICU rooms are being implemented in hospitals across the United States, particularly in newly constructed units.⁶² Studies examining private-room ICU implementation have typically been conducted by investigators in countries outside the United States, including Canada, China, the European Union, and Israel.^{59,61,63,64} One physician asserts this is because investigators in these nations have access to information on longevity and other outcomes from their nationalized health care systems, making their findings more informative.⁶²

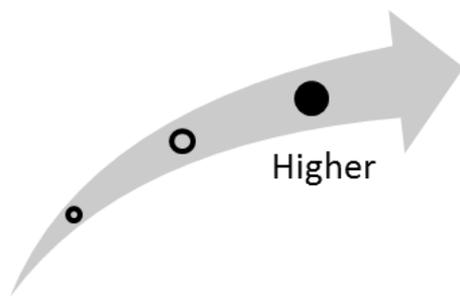
Diffusion: Although patients may prefer private ICU rooms, these rooms are more costly to build and staff than semiprivate rooms. Some researchers stated that building single-patient ICU rooms cost millions of dollars;⁵⁹ however, according to one cost-benefit analysis of inpatient private rooms versus semiprivate rooms, the net social benefit of a private room was estimated at about \$70,000 relative to a semiprivate room. Investigators believe that considering societal costs is important because hospitals are costly, long-term investments for the community that, once constructed, are extremely expensive to renovate.⁶⁵

Third-party payers are not expected to provide additional reimbursement for private rooms.⁶² Additional costs for private rooms are expected to be absorbed by the facility and could possibly lead to additional out-of-pocket expense for patients.

Clinical Pathway at Point of This Intervention

Patients are admitted to an ICU for the long-term care of serious, life-threatening conditions (i.e., cardiovascular disease, pulmonary disease, renal disease, serious gastrointestinal disorders, stroke or encephalopathy, infections or sepsis, organ failure or severe trauma).⁶⁶ Severe infections are common in ICUs and risk increases with length of stay.⁶⁷ Retrofitting existing multiple-bed ICU room designs with single-patient rooms could reduce the rate of HAIs in this patient population.

Figure 3. Overall high-impact potential: retrofitted private intensive care rooms to reduce hospital-acquired infections



Overall, experts concluded that results from the available studies of retrofitting ICUs with private rooms are promising. Experts thought that this design approach has significant potential to address the unmet need of reducing HAIs when combined with other best practices for infection control. Experts agreed that significant capital investment would be required for infrastructure and equipment for private rooms; however, the experts thought reductions in HAIs and associated liability would eventually be cost-saving. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.⁶⁸⁻⁷³ We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: HAIs cause great morbidity, mortality, and costs to the health care system, noted experts commenting on this intervention. The burden of HAI on patients who are already in critical condition is often life threatening. Also, antibiotic resistance is making HAIs tougher to treat, making HAI prevention a high unmet need, the experts stated. Private ICU rooms have been shown to significantly reduce the incidence of HAI and are an important consideration when remodeling or renovating hospital wings, most experts agreed. However, one expert representing a research perspective stated that the study designs and conduct of the existing data enable only weak conclusions from these data. Additionally, experts stated that private ICUs will not eliminate all HAIs; one health systems expert noted that the intervention should be only one component of a comprehensive HAI reduction campaign. Another health systems expert cautioned that many ICU patients have serious comorbid conditions irrespective of the HAI threat, and large improvements in patient health outcomes might not be observed with the intervention. Reductions

in length of stay and multiple subdiagnosis are expected to be the best endpoints to measure the impact of private rooms, the health systems expert noted.

Acceptance and adoption: Clinicians are expected to appreciate better infection control as well as the ease of communicating freely with patients in private rooms, health systems experts noted. Patients are expected to readily accept private ICU rooms as a standard, particularly if having a patient roommate exposes the ICU patient to additional risk, one expert noted. Patients are also expected to welcome being in a more private setting for communication with family and clinicians. However, one barrier to patient acceptance could be additional out-of-pocket costs if third-party reimbursement does not cover additional costs and hospital charges increase, two experts noted.

Health care delivery infrastructure and patient management: Renovations for private rooms would require significant investment in infrastructure, some experts stated, and private ICU rooms could require additional staff to monitor rooms that are farther apart, or the intervention could increase response time. However, one health systems expert stated that patients need care for their medical conditions, and adjusting to private rooms should not be an issue for facilities that are already focused on quality care. Private ICU rooms are expected to reduce the amount of care needed by reducing HAI incidence and improving health outcomes, one health systems expert stated. Overall, the experts theorize that private ICU renovations would be cost-saving over time.

Health disparities: Private ICU rooms could increase health disparities because rural hospitals and community health centers may not have the resources for ICU renovations. Additionally, some experts noted that if a choice exists between private and shared ICU rooms, there may be higher out-of-pocket costs for the patient to have a private room, assuming similar rates of reimbursement, which could create disparities.

Xpert MTB/RIF Test for Simultaneous Detection and Drug-Sensitivity Testing of *Mycobacterium Tuberculosis*

Unmet need: According to the World Health Organization, tuberculosis (TB) is highly underdiagnosed. This is a direct result of current TB testing methods, which require weeks to deliver a definitive result; during that time, patients are not treated or placed on ineffective therapies. These patients may also continue to spread TB to others in the community, creating a significant public health concern.⁷⁴

Intervention: The *Mycobacterium tuberculosis*/rifampicin test (Xpert[®] MTB/RIF) is a nucleic acid–based test run on the GeneXpert[®] real-time polymerase chain reaction (PCR) system.⁷⁴ The test simultaneously detects the presence of *M. tuberculosis* complex species and determines whether the identified bacterium is susceptible to rifampicin, the first-line TB drug.⁷⁵

In the assay, a real-time hemi-nested PCR reaction is performed to amplify and detect a portion of the *rpoB* gene, a genetic marker that is specific for a subunit of an RNA polymerase essential to TB viability.⁷⁴ The antibiotic activity of rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.⁷⁴ Research has demonstrated that the portion of the *rpoB* gene amplified in the Xpert MTB/RIF assay harbors mutations in the majority of rifampicin-resistant TB strains.⁷⁶

In the assay, the detection of TB DNA in the patient sample is accomplished by five separate real-time PCR fluorescent probes, which are specifically activated in the presence of amplified *rpoB* DNA and detected by the GeneXpert system.⁷⁵ Each of the five probes overlaps a different site known to be mutated in rifampicin-resistant TB if rifampicin resistance can be determined based on the binding signal given from the probes.⁷⁵

To perform the test, a technician first treats a patient sputum sample with a solution containing sodium hydroxide and isopropanol (isopropyl alcohol) to reduce the viability of any *M. tuberculosis*, thereby preventing contamination. Subsequent processing and detection are performed on the GeneXpert system using a single-use, closed Xpert MTB/RIF cartridge that contains all the reagents necessary for testing.^{74,75} The procedure's automated nature and the fact that it does not require handling of PCR amplicons are intended to ensure optimal accuracy of the assay by limiting interoperator variability and reducing the potential for false positives caused by amplicon contamination.⁷⁵ The assay is intended to yield results for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples in about 2 hours.⁷⁴ For a clinician to fully determine an effective treatment regimen, full drug-susceptibility testing would still need to be performed in patients with rifampicin-resistant TB.

Clinical trials: In a diagnostic substudy of a TB prevalence survey conducted in gold mining companies in South Africa, participants' sputum (n=6,893) was tested using liquid culture (reference comparator), Xpert MTB/RIF, and smear microscopy. Sputum samples tested positive for *M. tuberculosis* in 2.7% of samples tested by culture, 2.1% of samples tested by the Xpert MTB/RIF test, and 1.3% of samples tested by microscopy. Sensitivity for the test was 62.6%, specificity was 99.6%, positive predictive value was 81.3%, and negative predictive value was 98.9%. Agreement between Xpert and culture was 98.5%. Sensitivity of microscopy was 17.6%. When individuals with a history of TB treatment were excluded from the analysis, Xpert MTB/RIF specificity was 99.8% and the positive predictive value was 90.6% for detecting *M. tuberculosis*. Costs for testing the 7,000 specimens, with 2.7% of specimen cultures positive for *M. tuberculosis*, were \$165,690 for Xpert MTB/RIF and \$115,360 for the combination of microscopy and culture.⁷⁷

In a large multicenter trial, patients (18 years of age or older) suspected of having TB or multidrug-resistant TB (n=6,648) presenting with cough lasting at least 2 weeks were tested for TB

using Xpert MTB/RIF, culture, and microscopy detection methods. The investigators reported, “One-off MTB/RIF testing detected 933 (90.3%) of 1033 culture-confirmed cases of tuberculosis, compared with 699 (67.1%) of 1041 for microscopy. MTB/RIF test sensitivity was 76.9% in smear-negative, culture-positive patients (296 of 385 samples), and 99.0% specific (2846 of 2876 non-tuberculosis samples).” The sensitivity and specificity of the MTB/RIF test for rifampicin resistance were 94.4% and 98.3%, respectively. As observed with microscopy, MTB/RIF test sensitivity was not significantly lower in patients co-infected with HIV. Median time to detection of TB was 0 days for the MTB/RIF, 1 day for microscopy, 16 days for liquid culture, and 30 days for solid culture. Using the MTB/RIF test reduced the median time to treatment of patients with smear-negative TB from 56 days to 5 days.⁷⁸

In an international clinical trial, investigators collected three sputum samples each from patients suspected of having TB or drug-resistant TB (n=1,730). Samples were analyzed by a combination of acid-fast smear, solid culture, liquid culture, and Xpert MTB/RIF tests. Among culture-positive patients, the Xpert MTB/RIF test gave a positive TB result for 551 of 561 smear-positive patients (98.2%) and for 124 of 171 smear-negative patients (72.5%). Additionally, among 609 culture-negative patients, the Xpert MTB/RIF test correctly identified 604 patients as negative for TB infection (99.2%). As for susceptibility testing, compared with conventional culture-based susceptibility testing, the Xpert MTB/RIF test correctly identified 200 of 205 patients with TB as having a rifampicin-resistant infection (97.6%) and 504 of 514 patients with TB as having a rifampicin-sensitive infection (98.1%).⁷⁹

In an additional study, investigators compared Xpert MTB/RIF to culture and microscopy detection methods using samples from pediatric patients with suspected TB (n=164). Xpert MTB/RIF detected 100% of the smear-positive cases and 66.6% of culture-positive cases that were smear negative. In the per-sample analysis, Xpert displayed a similar sensitivity to culture methods and detected threefold more confirmed TB cases than microscopy in a similar amount of time. Four additional culture-negative cases with clinical TB (8.5%) were diagnosed by Xpert MTB/RIF. Xpert MTB/RIF demonstrated 100% specificity when TB was reliably excluded; accuracy was not affected by HIV infection in these patients.⁸⁰

In a randomized, multicenter trial, patients suspected of TB presenting at five primary health care facilities in South Africa, Zimbabwe, Zambia, and Tanzania were evaluated at the point-of-care using either Xpert MTB/RIF (n=744) or sputum smear microscopy (n=758). Patients with a negative test result were empirically managed according to local World Health Organization–adherent guidelines. Point-of-care Xpert MTB/RIF had higher sensitivity than smear microscopy (83% vs. 50%; p=0.0001) but similar specificity (95% vs. 96%; p=0.25).⁸¹ Xpert MTB/RIF point-of-care testing had similar sensitivity to laboratory-based Xpert MTB/RIF testing (83%; p=0.99) and higher specificity (92%; p=0.0173). Five percent of point-of-care Xpert MTB/RIF tests failed compared with 6% of laboratory-run Xpert MTB/RIF tests (p=0.22).⁸¹ More patients tested with MTB/RIF had a same-day diagnosis compared with microscopy (24% vs. 13%; p<0.0001) and more patients initiated same-day treatment (23% vs. 15%; p=0.0002). However, by day 56, the proportions of patients receiving therapy were similar for Xpert MTB/RIF and microscopy (43% vs. 42%; p=0.6408).⁸¹

Manufacturer and regulatory status: Cepheid (Sunnyvale, CA) makes the Xpert MTB/RIF test.⁷⁴ In July 2013, FDA granted Cepheid marketing approval for the Xpert MTB/RIF test through the de novo classification process. The de novo classification is a regulatory pathway for medical devices that are considered generally of low to moderate risk but have no comparable predicate device.⁸² Xpert MTB/RIF is indicated for the rapid molecular detection of *M. tuberculosis* complex

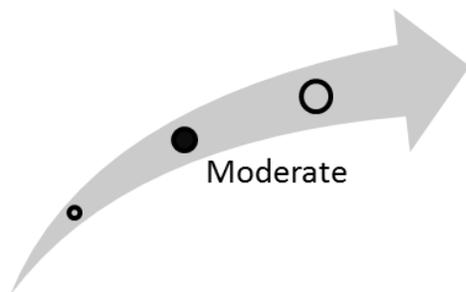
DNA as well as the detection of rifampin resistance associated with mutations of the *rpoB* gene in specimens positive for *M. tuberculosis*.⁸²

Diffusion: Pricing for the Xpert MTB/RIF test is not available; however, other test cartridge-based assays running on the GeneXpert system cost approximately \$20 per assay.⁸³ Additionally, to run the Xpert MTB/RIF test, a facility would need to have a GeneXpert system, which could represent a capital equipment purchase of more than \$100,000 for higher throughput versions.^{74,84} According to one source, standard basic testing for TB costs about \$20–\$40, and more advanced testing to determine rifampicin resistance can add another \$20–\$30.⁸³ This test would likely be billed using current TB codes. In August 2013, FDA categorized the Xpert MTB/RIF test as “moderate complexity” under the Clinical Laboratory Improvement Amendments (CLIA), which could facilitate diffusion.⁸⁵

Clinical Pathway at Point of This Intervention

A patient initially presents with symptoms that indicate a possible case of pulmonary TB based on his or her medical history, physical examination, symptoms, TB infection test results (e.g., tuberculin skin test, QuantiFERON-TB Gold test), and/or chest radiographs.^{86,87} The current recommended diagnostic procedure for laboratory confirmation of TB is to obtain a respiratory sputum sample from the patient and test the sample simultaneously with a nucleic acid amplification test, an acid-fast bacteria smear test, and liquid or solid media culture.⁸⁶ The Xpert MTB/RIF test would be used in place of current nucleic acid amplification tests. Besides identifying the presence of TB, the Xpert MTB/RIF test would also give a preliminary indication of potential antibiotic resistance, which would normally be determined following a positive culture isolate by assaying the isolate’s in vitro susceptibility to antibiotics.^{74,86}

Figure 4. Overall high-impact potential: Xpert MTB/RIF test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis*



Overall, experts commenting on this intervention thought that the Xpert MTB/RIF test has potential to be a rapid, sensitive, and specific diagnostic that could address the unmet need for more rapid diagnosis and better initial management of TB. They thought it has potential to improve patient health outcomes and reduce the spread of TB. By knowing the patient’s TB status before he or she leaves the physician’s office, experts noted, more appropriate treatment could be given and proper infection control measures could be implemented. However, the Xpert MTB/RIF test detects resistance only to rifampin, a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR detection methods and provide an improved approach to diagnosis and treatment, which could reduce problems with followup of patients who have limited access to care. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁸⁸⁻⁹⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current TB diagnostic methods are lengthy, taking days to weeks to confirm or rule out the presence of TB and antibiotic susceptibility, the experts concurred. This, they said, represents a significant unmet need for more rapid diagnostic testing to direct appropriate therapy and implement infection control measures for patients, the community, and health care providers. Experts agreed that the Xpert MTB/RIF test is fast and accurate, which allows health care practitioners to implement infection control procedures almost immediately. Additionally, the test provides early detection of rifampicin resistance to guide appropriate antibiotic selection, which could improve health outcomes.

Acceptance and adoption: Although most experts thought that clinicians would readily embrace Xpert MTB/RIF testing, one expert representing a research perspective stated that facilities using other PCR methods may resist early adoption because only 1% of the TB cases in U.S.-born patients have multidrug-resistant TB. Patients were expected to embrace rapid diagnosis.

Health care delivery infrastructure and patient management: In general, the experts thought the Xpert MTB/RIF test would not have a large impact on how the disease is treated or diagnosed but that it would allow current treatment strategies to be employed earlier and, therefore, potentially reduce disease transmission. Although experts thought impact on staffing and training would be minimal, a significant capital investment of \$100,000 is required to purchase the GeneXpert system if the facility has not purchased it for other testing. An expert with a research perspective stated that Xpert MTB/RIF testing will likely be cost effective. However, initial costs of the GeneXpert system could lead to more centralized TB testing centers.

Health disparities: The Xpert MTB/RIF assay could improve health disparities because it is inexpensive for patients, the experts stated, and most thought that Xpert MTB/RIF testing would be offered in most emergency departments and public health clinics. However one expert representing a research perspective stated that the GeneXpert system may be too costly in some underserved areas, which could create disparities.

Hepatitis C Virus Infection Intervention

Sofosbuvir (Sovaldi) for Treatment of Chronic Hepatitis C Infection

Unmet need: In May 2011, two novel treatments were FDA approved for treating hepatitis C virus (HCV) infection: NS3/4a protease inhibitors boceprevir and telaprevir. They were approved for use in combination with interferon alfa (IFN) and ribavirin (RBV) for treating chronic hepatitis C genotype 1 infection.^{95,96} Protease inhibitor therapy can improve cure rates for chronic hepatitis C, genotype 1, in both treatment-naïve and treatment-experienced patients compared with IFN/RBV alone.^{95,96} However, up to half of patients with chronic HCV infection are not candidates for these triple therapy options.⁹⁷ Also, protease inhibitors are associated with significant side effects including anemia and severe rash.⁹⁸ Lastly, approved protease inhibitors are effective against only HCV genotype 1 infection. Effective, well-tolerated, IFN-free treatment options that are pan-genotypic are needed for treating chronic HCV infection.⁹⁷

Intervention: Sofosbuvir (Sovaldi™) is a uridine nucleotide analog polymerase inhibitor in phase III trials for treating chronic HCV infection.^{98,99} The HCV NS5B polymerase plays an essential role in HCV genome replication. As a nucleotide analog, sofosbuvir is said to target the active site of the enzyme and inhibit elongation of the growing HCV RNA genomic transcript.⁹⁸ Nucleos(t)ide analogs such as sofosbuvir are thought to have broader efficacy against different HCV genotypes and a higher barrier to viral resistance than nonnucleos(t)ide polymerase inhibitors, which function via allosteric inhibition.⁹⁸

Sofosbuvir is being evaluated as part of multiple therapeutic regimens. It is administered orally, 400 mg once daily, for 12 weeks in combination with RBV for patients infected with HCV genotype 2 and for 24 weeks for patients infected with genotype 3, and for 12 weeks with IFN and RBV for patients chronically infected with HCV genotypes 1 or 4.¹⁰⁰ Sofosbuvir has also been evaluated in combination with other direct-acting antiviral agents, including a once-daily fixed-dose combination with the NS5A inhibitor ledipasvir, in an effort to create a convenient all-oral treatment that would eliminate the need for IFN and/or RBV in patients with chronic HCV genotype 1 infection.^{98,99}

Clinical trials: In a phase III, randomized controlled trial, patients (n=499) with chronic HCV genotype 2 or 3 infection who had not received prior treatment were given either 12 weeks of sofosbuvir (400 mg, once daily) and RBV (1,000 or 1,200 mg/day) or 24 weeks of IFN (180 mcg/week) and RBV (800 mg/day). Sofosbuvir plus RBV met the primary endpoint of non-inferiority to IFN/RBV, with 67% of patients achieving a sustained viral response (SVR) in both groups. The SVR rates at week 12 (SVR12) in patients receiving sofosbuvir plus RBV were 97% and 56% for patients infected with genotype 2 and genotype 3, respectively. The SVR12 rates in patients treated with IFN/RBV were 78% and 63% for patients infected with genotype 2 and genotype 3, respectively. Of patients treated with sofosbuvir, 20% had compensated cirrhosis, and of patients treated with IFN/RBV, 21% had compensated cirrhosis.¹⁰¹

Another phase III, randomized controlled trial evaluated the safety and efficacy of sofosbuvir in patients with chronic HCV genotype 2 or 3 infection for whom IFN treatment was not an option. Patients received sofosbuvir and RBV (n=207) or placebo (n=71) for 12 weeks. Patients treated with sofosbuvir and RBV achieved an SVR of 78% compared with 0% in the placebo group (<0.001).¹⁰²

In a third, phase III, single-arm trial, patients (n=327) with HCV genotype 1, 4, 5, or 6 and no prior treatment were given sofosbuvir (400 mg once daily) in combination with RBV (1,000 or 1,200 mg/day) and IFN (180 mcg/week) for 12 weeks. Patients treated with sofosbuvir met the primary efficacy endpoint of superiority as compared with a predefined historic control (90% of

patients achieved SVR12 vs. 60% of historic control patients [$p < 0.001$]). Patients had primarily HCV genotype 1 (89%), and SVR12 was 89%.¹⁰¹ SVR12 was achieved in 97% of patients with genotypes 4, 5, or 6 treated with sofosbuvir. Compensated cirrhosis was present in 17% of patients in the trial, and 80% of these patients achieved SVR12.¹⁰¹

In a phase III, open-label trial, patients ($n=182$) co-infected with HIV and HCV (genotypes 1, 2, or 3) who were naïve to HCV treatment were given sofosbuvir (400 mg once daily) and RBV. After 24 weeks of therapy, 78% of patients infected with HCV genotype 1 ($n=114$) achieved an SVR12. After 12 weeks of therapy, patients infected with HCV genotype 2 ($n=26$) and genotype 3 ($n=42$) achieved SVR12 rates of 88% and 67%, respectively.¹⁰³

In studies in which patients were given sofosbuvir and RBV, the most common side effects reported were dizziness, fatigue, headache, insomnia, and nausea.¹⁰² When patients were given sofosbuvir in combination with IFN/RBV, the most common side effects reported were anemia, fatigue, headache, insomnia, and nausea.^{101,104}

Manufacturer and regulatory status: Gilead Sciences, Inc., of Foster City, CA, makes sofosbuvir. In April 2013, the company filed a new drug application with FDA for sofosbuvir for treating chronic HCV infection. In December 2013, FDA approved sofosbuvir in combination with RBV for treating patients infected with HCV genotypes 2 or 3 and in combination with IFN/RBV for treating patients infected with HCV genotype 1 or 4. Sofosbuvir is also approved for treating patients co-infected with HIV or with hepatocellular carcinoma awaiting liver transplantation.^{100,105}

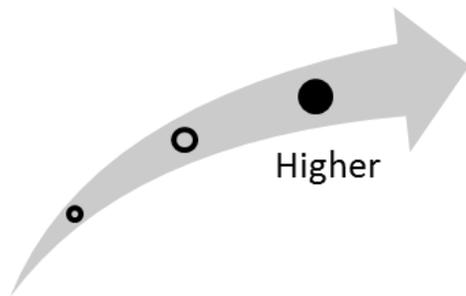
Diffusion: Sofosbuvir costs about \$84,000 for a 12 week treatment course.¹⁰⁶ For benchmarking purposes, a standard 12-week treatment regimen of the protease inhibitor telaprevir is about \$50,000.¹⁰⁷ Boceprevir, also a protease inhibitor, costs about \$1,100 per week of treatment with treatment duration ranging from 24 to 44 weeks depending on patient characteristics.^{95,108} Thus, the cost of typical boceprevir therapy regimens ranges from about \$26,000 to about \$48,000.^{107,108}

Sofosbuvir is expected to be covered by payers because of the unmet safety and efficacy need despite existing IFN-based treatments. Third-party payers typically cover HCV protease inhibitors as specialty tier drugs requiring prior authorization for coverage.¹⁰⁹⁻¹¹⁹ Sofosbuvir will likely be treated in a similar manner.

Clinical Pathway at Point of This Intervention

Patients who test positive for HCV and HCV RNA may be considered to have acute or chronic HCV infection, depending on the context. A patient who tests negative for antibodies to HCV and positive for HCV RNA might be chronically infected if immunosuppressed.¹²⁰ Subsequent HCV genotype testing is performed to determine the therapy regimen and likelihood of a positive clinical outcome.¹²⁰ Rest and hydration are typically prescribed. In 2011, the American Association for the Study of Liver Diseases updated its clinical practice guidelines to recommend treating patients with HCV-1 infection with a protease inhibitor (boceprevir or telaprevir) in combination with IFN/RBV.¹²¹ Sofosbuvir is indicated for use in combination with RBV for patients infected with HCV genotypes 2 or 3 and in combination with IFN/RBV for patients infected with genotypes 1 or 4. Sofosbuvir could also be used in combination with other investigational HCV agents such as ledipasvir) for treating patients infected with genotypes 1, 2, 3, 4, 5, or 6.

Figure 5. Overall high-impact potential: Sofosbuvir (GS-7977) for treatment of chronic hepatitis C infection



Overall, experts commenting on this intervention regarded sofosbuvir as having high potential to address significant unmet needs for HCV treatment. Sofosbuvir used as part of an all-oral regimen to treat chronic HCV infection is purported to have high efficacy that is well-tolerated by patients who cannot tolerate IFN or do not want to use IFN. Sofosbuvir also provides a shorter and simpler dosing regimen than current treatment options. The high efficacy of sofosbuvir thus far in HCV genotypes other than genotype 1 is also perceived to be a significant advantage that increases the drug's potential impact. Additional research is needed to determine the long-term impact of sofosbuvir therapy on rates of cirrhosis, liver cancer, and liver transplantation. Based on this input, our overall assessment is that this intervention is in the high end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, commented on this intervention.¹²²⁻¹²⁷ We have organized the expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A large cohort of aging patients chronically infected with HCV exists in the United States, experts pointed out. Many of these patients have advanced liver disease or are otherwise unable to tolerate an IFN-containing regimen and are in need of effective, new IFN-free treatment options that are well tolerated, the experts thought. Clinical cure of HCV infection is associated with improved health outcomes in patients, the experts stated. Basing their opinion on available evidence, the experts all thought sofosbuvir appears to be promising for treating chronic HCV infection. Sofosbuvir could also improve health outcomes for those with HCV genotypes that are not addressed with protease inhibitor therapy, the experts concluded.

Acceptance and adoption: Experts expect clinician acceptance of sofosbuvir to be high because of its high efficacy and safety shown so far. According to one clinical expert, protease inhibitors have already increased clinician willingness to initiate HCV treatment, and an easier treatment option will further increase treatment rates. The pan-genotypic activity of sofosbuvir is also expected to increase physician acceptance and adoption, noted one health systems expert. Patients are also expected to have a high acceptance of sofosbuvir because of its efficacy and tolerability, all-oral administration, and IFN-free treatment regimen. Although the high estimated cost of sofosbuvir therapy could to pose a barrier to diffusion for some patients, the upfront cost is expected to be offset by costs savings to the health care system by preventing the need for additional treatment, HCV complications, and health monitoring in the future, some experts commented.

Health care delivery infrastructure and patient management: The IFN-free treatment option that the drug could provide might entice more patients to seek HCV testing and treatment, some experts thought. Improved treatment outcomes could reduce hospitalizations from liver disease and

ease the burden on infrastructure and staffing for HCV inpatient treatments, one health systems expert stated, but other experts expected minimal disruptions to infrastructure and management with use of sofosbuvir compared with current treatment options.

Health disparities: An effective, well-tolerated, and simpler treatment regimen might reduce health disparities and would be likely to be covered by public and private payers, one clinical expert thought. Another clinical expert commented that because HCV may disproportionately affect marginalized populations because of risk factors for infection, effective treatment would improve health outcomes in these patients and, thus, reduce health disparities. But other experts pointed to the anticipated high cost of therapy as a possible barrier to sofosbuvir treatment.

HIV/AIDS Interventions

Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection

Unmet need: An estimated 1.2 million people in the United States are living with HIV infection, and 20% of those individuals are unaware of their HIV status.¹²⁸ CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 61% of new infections occur in men who have sex with men (MSM) and 23% occur in women;¹²⁹ women are twice as likely as men to be infected with HIV through heterosexual contact.¹²⁸ One estimate of the HIV transmission risk during receptive anal sex without a condom—the highest-risk sexual activity—indicates that it may be as high as 3% to 5% for each occurrence. The risk is estimated to be lower for receptive vaginal intercourse and even lower for oral sex, each in the absence of a latex barrier (condom or dental dam). Although no single sexual exposure carries a high risk of contagion, HIV infection can occur after the first sexual exposure; therefore, use of latex barriers during each sexual encounter is recommended.¹³⁰

Although behavior-change programs have resulted in dramatic reductions in HIV transmission in the United States, there remains no truly effective means to prevent HIV infection among populations at high risk for infection, including male prostitutes who have sex with men. Preexposure chemoprophylaxis (i.e., pretreating uninfected individuals at risk of contracting HIV infection with antiretroviral therapies [ARTs]) is an emerging intervention for reducing HIV transmission.¹³¹ Evidence has accumulated to support the theory that ART, taken regularly, can reduce the risk of HIV infection.¹³¹⁻¹³⁴

Intervention: Emtricitabine/tenofovir (Truvada[®]), which initially received FDA approval in 2004 to treat HIV infection, was reevaluated as part of a comprehensive strategy for preventing HIV in adults at high risk of infection.^{131,132} Emtricitabine/tenofovir is a once-daily, oral, combination ART consisting of two HIV nucleoside reverse transcriptase inhibitors, emtricitabine (Emtriva[®]) 200 mg and tenofovir disoproxil fumarate (Viread[®]) 300 mg, made by the same manufacturer.¹³⁵ Emtricitabine and tenofovir are also available separately in single-agent tablets. However, the combination of two nucleoside reverse transcriptase inhibitors in a single tablet taken once daily decreases patient pill burden and is believed to result in higher adherence to medication regimens among patients with HIV.¹³⁶ Treatment adherence is thought to be essential for high efficacy.¹³¹

Nucleoside reverse transcriptase inhibitors suppress replication of retroviruses by blocking the activity of HIV-1 reverse transcriptase.¹³⁵ This results in premature termination of viral DNA replication.

Clinical trials: In the Preexposure Prophylaxis Initiative (iPrEx) trial, HIV-seronegative men or transgender women who have sex with men (n=2,449) were prophylactically given emtricitabine/tenofovir or placebo once daily. The prophylactic use of emtricitabine/tenofovir was shown to lead to a 44% reduction in the incidence of HIV (95% CI, 15 to 63; p=0.005).¹³¹

In another trial, daily prophylactic use of emtricitabine/tenofovir failed to prevent HIV-1 infection in high-risk women. The study was stopped early due to lack of efficacy, which could have been due to low treatment adherence.¹³⁷

In a different trial of HIV-1–uninfected heterosexual men and women in Botswana who were 18–39 years of age (n=1,219), daily prophylactic use of emtricitabine/tenofovir reduced the risk of acquiring HIV infection by roughly 62% compared with infection rates with placebo.¹³⁸

An additional analysis that excluded HIV infections that occurred more than 30 days after a participant's last reported drug dose was conducted because these individuals could not have been taking study pills at the time of infection. In this analysis, emtricitabine/tenofovir reduced the risk of HIV infection by 78% compared with infection rates with placebo.¹³³

In another trial examining HIV-1–serodiscordant heterosexual couples in Kenya and Uganda (n=4,758), patients who took daily prophylactic tenofovir had an average 67% fewer infections

($p < 0.001$) than those who received placebo; patients who took prophylactic emtricitabine/tenofovir had an average 75% fewer infections ($p < 0.001$). There was no significant difference between the protective effects of tenofovir and emtricitabine/tenofovir ($p = 0.23$).¹³⁹

Patients prescribed preexposure prophylaxis (PrEP) must be confirmed to be HIV-negative immediately before initial use and periodically during use to prevent the development of drug resistance. The manufacturer says that PrEP should not be initiated if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.¹³⁵

The most common adverse events associated with emtricitabine/tenofovir for PrEP include abdominal pain, headache, and weight loss.¹³⁵ The manufacturer states that patients should be tested for hepatitis B virus before initiating PrEP because severe acute exacerbations of hepatitis B have occurred in patients co-infected with HIV-1 and hepatitis B virus who have discontinued emtricitabine/tenofovir.¹³⁵ Patients taking PrEP should be evaluated for new onset or worsening renal impairment. Emtricitabine/tenofovir use has also been associated with decreased bone mineral density and with body fat redistribution or accumulation.¹³⁵

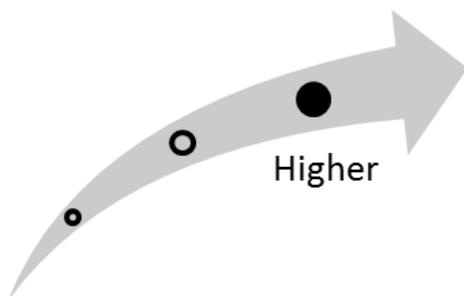
Manufacturer and regulatory status: Gilead Sciences makes emtricitabine/tenofovir. In July 2012, FDA approved emtricitabine/tenofovir once daily in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.¹⁴⁰

Diffusion: The retail cost of a 30-day supply of emtricitabine/tenofovir is roughly \$1,300.¹⁴¹ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that only Aetna and United Healthcare list coverage determinations specifically for PrEP; both payers state they will cover PrEP when the drug is prescribed consistently with its indication.^{142,143} According to the manufacturer, patients with insurance who are prescribed emtricitabine/tenofovir for treating chronic HIV infection commonly have a \$10 copayment.¹⁴⁴

Clinical Pathway at Point of This Intervention

According to clinical practice guidelines, the most reliable way to avoid HIV transmission is to abstain from sexual contact or to be in a long-term, mutually monogamous relationship with an uninfected partner. For those entering a monogamous relationship, HIV screening before initiating sex may reduce the risk of future HIV transmission. Male latex condoms are also highly effective at preventing HIV-1 transmission. In people with latex allergy, nonlatex male condoms made of polyurethane or other synthetic material provide protection against HIV equal to that of latex condoms.¹⁴⁵ Emtricitabine/tenofovir is a combination ART under clinical development for preventing HIV-1 transmission in patients at high risk of contracting HIV infection.

Figure 6. Overall high-impact potential: emtricitabine/tenofovir (Truvada) for prevention of HIV infection



Overall, experts commenting on this intervention thought that prophylactic use of this drug has high potential to address an important unmet need as the first pharmacologic agent approved for reducing the risk of HIV-1 infection in high-risk patients. No other preventive medication options are available; abstinence and condom use are effective but are not employed by all individuals at high risk of infection. Experts thought that emtricitabine/tenofovir could have a large impact on health promotion by reducing the number of HIV-infected individuals. However, experts cited the early trials that have shown this intervention would not protect everyone who attempts the regimen. This, combined with high treatment costs and likely high out-of-pocket costs to patients for something that is not a disease (i.e., unprotected sex) and that can be prevented with behavior interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves. The experts stated that public-private partnerships will be essential for providing the medication, education, and followup necessary to effectively implement PrEP and improve health outcomes in all eligible patients. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, commented on this intervention.¹⁴⁶⁻¹⁵² We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need remains for effective measures to prevent HIV transmission in serodiscordant couples, the experts stated. Additionally, they noted that some individuals at high risk are not in a position to practice all safer sex measures during each sex act. Before FDA approval of emtricitabine/tenofovir, no pharmacologic methods were available to reduce the risk of HIV infection, which represented a significant gap in HIV risk mitigation. Overall, experts stated that PrEP with emtricitabine and tenofovir could fill a significant unmet need, because it is the first approved pharmacotherapy intended to reduce the risk of acquiring HIV in patients at high risk of infection.

Health outcomes could improve if PrEP significantly reduces the risk of contracting HIV, the experts thought. However, they expressed some pessimism about the need for high treatment-adherence to achieve optimal protection. Experts also speculated that the lack of efficacy in protecting women might be due to the drug's inability to concentrate sufficiently in vaginal tissue, which is where transmission occurs during intercourse. They also speculated lack of efficacy might be due to problems with treatment adherence, and others hypothesized that during one trial, women may have given their HIV medication to their infected partners instead of taking it themselves.

Acceptance and adoption: Experts were divided regarding patient and clinician acceptance of PrEP. One clinical expert stated that primary care physicians rarely ask sex and sexuality questions of their patients, which would make it difficult to identify patients at high risk of infection. These physicians could also be reluctant to familiarize themselves with the protocols necessary to properly implement PrEP. Other experts thought clinicians could be reluctant to recommend PrEP because they think it might increase risky behavior, that it could cause side effects in otherwise healthy patients, or that their patients would be unable to afford it. Cost was also cited as a barrier to patient acceptance, and experts noted other barriers to patient acceptance, including being stigmatized for seeking HIV therapy and being unable to adhere to quarterly followup. Further, one expert stated that patients routinely underestimate their personal level of exposure risk, which would make them less likely to seek PrEP. However, some experts stated that in the appropriate patient population, PrEP could be highly accepted by both patients and clinicians.

The experts stated that PrEP is a costly intervention. However, it could be cost saving in some populations. But even if it is found to be cost saving and third-party payers cover PrEP in the future, some patients could still be reluctant to admit that they are at high risk for HIV infection, because this admission could increase their insurance premiums.

Health care delivery infrastructure and patient management: PrEP is expected to disrupt health care infrastructure and patient management by shifting HIV prevention to primary care physicians and obstetricians or gynecologists who are not familiar with prescribing PrEP, monitoring the side effects of emtricitabine/tenofovir, or performing HIV testing quarterly. Additionally, primary care physicians and obstetricians/gynecologists are not familiar with teaching their patients about HIV risk mitigation strategies, which could require some training. If PrEP is successful, less demand on staff and facilities to treat HIV infection could be realized.

Although the intervention is controversial because of its high cost and because clinicians prescribe a pharmaceutical to prevent a disease that patients can address with behavior interventions, the experts stated that PrEP is a major step forward in the battle against HIV/AIDS. The experts stated that public-private partnerships will be essential to providing the medication, education, and followup necessary to effectively implement PrEP and in improving health outcomes in all eligible patients.

OraQuick In-Home Rapid Test for Detection of HIV Infection

Unmet need: According to a CDC study, about half of all new HIV infections occur from the approximate 20% of persons living with HIV who are unaware of their infection. Additionally some HIV screening methods can take up to 2 weeks before patients are made aware of their HIV status.¹⁵³ Although an over-the-counter HIV test has been available since 1996, it requires that a blood sample be mailed to a laboratory for analysis and results are available the next business day at the earliest. A simple, rapid, in-home test, such as the OraQuick® In-Home HIV Test, that patients can interpret, might improve HIV-screening rates by increasing the privacy and confidentiality of testing, empowering individuals to make health decisions, and providing a more rapid assessment of HIV sero-status without the need for individuals to follow up seronegative test results.¹⁵⁴ Increased screening could reduce HIV transmission rates and improve disease management through earlier treatment.^{155,156}

Intervention: The OraQuick In-Home HIV Test is a rapid, home-based HIV test that is available without prescription, over the counter.¹⁵⁴ It is intended to improve HIV-screening rates in people at risk of HIV exposure by removing barriers to screening. The test provides easy access to first-line testing that is affordable, safe, simple, rapid, painless, and anonymous.¹⁵⁴ OraQuick is designed to detect HIV-specific antibodies found in a patient's saliva. The test kit includes a single-use testing device and a test tube containing testing reagent. The testing device is a lateral flow immunoassay with an integrated oral swab.

To initiate the test, people collect a saliva sample from along the gum line using the oral swab; they then place the swab end of the testing device in the test tube with reagent for 20 minutes.¹⁵⁴ For accurate results, people must not eat, drink, or use oral care products for at least 30 minutes before testing themselves.¹⁵⁷

The testing device contains colloidal gold particles bound to protein A, which will bind antibodies from the saliva sample in solution.¹⁵⁸ The antibody-bound colloidal gold particles migrate along the device, which has two indicator lines towards the distal end. The first indicator line contains HIV antigen that binds the antibody-bound colloidal gold particles only if the saliva sample has antibodies against HIV.^{154,158} Presence of HIV antibodies will lead to the generation of a reddish-purple color at the test line, indicating a qualitatively positive result. The second indicator line is an internal control that binds human immunoglobulin G to show that the test has been used properly and that antibodies are present in the sample.

The kit includes resources on HIV and HIV testing, including a hotline with 24-hour customer support to answer questions regarding testing and interpretation as well as referral to care if needed.¹⁵⁹ If a person tests negative for HIV and 3 months have passed since the last risk event, he or she is likely to be HIV negative.¹⁶⁰ If a person tests positive for HIV, followup is required at a health care facility at which infection must be confirmed by Western blot analysis.^{153,160}

The OraQuick home test is predicated on an oral swab-based test that has been available to health care professionals since 2004.¹⁶¹ Changes were made only to the packaging and instructions to create the home test version of the test; the manufacturer made no changes to the test device.¹⁶²

Clinical trials: In a large clinical trial used to support regulatory filing individuals (n=5,662) of unknown HIV status underwent HIV screening in a three-visit process. At the first visit, blood was drawn for HIV laboratory testing. At the second visit, unobserved self-testing with the OraQuick In-Home HIV test was offered; next, testing occurred at a location of the individual's choosing. Finally, at the third visit, the individual provided self-interpreted results of the at-home testing and were provided with laboratory testing results. A total of 96 participants were included in the sensitivity analysis, of which 88 were true positive determined by self-test and lab result if both gave positive result. Eight participants were determined to be false negative, reporting a negative

self-test result and having a positive laboratory result. Sensitivity of self-testing was 91.67% (95% CI, 84.24% to 96.33%).

A total of 4,903 participants were included in the specificity analysis. Of these, 4,902 participants were determined to be true negative because their self-test results and laboratory results were both negative. One subject was determined to have a false-positive self-test. Specificity was calculated to be 99.98% (95% CI, 99.89% to 100%).¹⁶²

A behavioral study was conducted to determine whether ethnically diverse MSM (n=27) considered at risk of contracting HIV infection who never or rarely used condoms would use the OraQuick In-Home HIV Test to screen potential sexual partners. Participants used home test kits before intercourse with about 100 partners in private and public spaces. Testing purportedly had high acceptability among participants representing ethnic minority populations. Ten individuals who were tested received a positive result; 7 HIV-positive individuals were potential sexual partners and 3 were acquaintances of the participants; 6 of the 10 individuals with a positive result were unaware of their status. No sexual intercourse occurred after positive tests results were received. Most participants expressed a strong desire to continue using the home test and to buy it freely.¹⁶³

The manufacturer warns that the test should not be used to make decisions on behavior that may put one at increased risk for HIV.¹⁶⁴ As with any diagnostic test, the OraQuick In-Home HIV test has the potential to produce false-negative or false-positive results. False-negative HIV test results could have adverse consequences for the individual tested, such as delayed treatment for HIV, which could limit treatment efficacy. Additionally, false-negative results could result in unsuspected HIV transmission in cases in which behavior is altered on the basis of the negative HIV test result. Conversely, false-positive results could result in patient anxiety and wasted health care resources in responding to a positive result for an HIV-negative patient.

Manufacturer and regulatory status: OraSure Technologies, Inc., of Bethlehem, PA, makes the OraQuick In-Home HIV Test. In July 2012, FDA approved the test for over-the-counter sale directly to consumers. The test can detect antibodies to both HIV-1 and HIV-2.¹⁵⁹ The test is the first and so far only rapid over-the-counter test approved by FDA for detecting HIV or any other infectious disease.¹⁵⁹ The test became commercially available in the United States in October 2012.¹⁶⁵

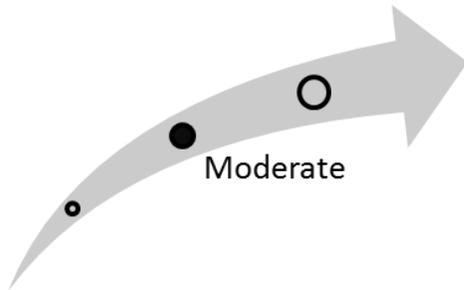
Diffusion: The test costs about \$40 when purchased directly from the manufacturer.¹⁶⁶ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that only Aetna lists a coverage determination for the HIV home test kits. Although Aetna covers physician-prescribed HIV testing, it “does not cover home HIV test kits that do not require a physician’s prescription under any of its plans.”¹⁶⁷ Most health plans do not cover over-the-counter health products.

Clinical Pathway at Point of This Intervention

CDC recommends testing for HIV at least once in individuals 13–64 years of age and annual testing for persons who engage in activities that put them at risk for infection, including sex (vaginal, oral, or anal) with multiple sex partners, sex with someone who is HIV positive or whose HIV status is unknown, sex between a man and another man, sharing needles or syringes (for illegal injected drugs or steroids), exchanging sex for money or drugs, or having a diagnosis of sexually transmitted infections or tuberculosis.^{155,156} Testing should occur 3 months after a high-risk event to ensure accurate detection of antibodies against HIV.^{153,156} HIV tests performed in health care facilities can consist of HIV enzyme immunoassays that detect HIV antibodies present in blood,

saliva, or urine. All positive HIV test results must be confirmed with a followup test, such as Western blot to rule out false-positive results. The OraQuick In-Home HIV Test could compete with the Home Access Express system, a home-based test that detects the presence of HIV antibodies in blood from a finger prick, which is placed on a sample card and mailed to a testing facility. The Home Access Express consumer calls a phone number to receive anonymous test results and counseling.¹⁶⁸

Figure 7. Overall high-impact potential: OraQuick in-home rapid test for detection of HIV infection



Overall, experts commenting on this intervention thought the OraQuick rapid in-home HIV test has potential to meet a significant unmet need by increasing HIV-screening rates in patients who engage in high-risk behaviors but are reluctant to undergo HIV screening in clinics. In-home testing, thought experts, could improve screening rates in patients who can afford the \$40 cost to purchase and perform testing. Experts stated that patients who know their HIV status are more likely to seek treatment and avoid high-risk behaviors, which could positively affect public health outcomes and reduce costs to the system, although an increase in the number of patients seeking treatment from positive test results would be expected to increase costs to the system. Patients presenting to a clinic with a positive at-home result will require confirmatory testing and perhaps counseling, thought experts; the OraQuick test has potential to reduce the number of “worried well” patients coming to clinicians for testing. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹⁶⁹⁻¹⁷⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The OraQuick in-home rapid test could fill a significant unmet need, increasing HIV detection rates by providing a private and convenient method of HIV testing and providing rapid results, the experts stated. One clinical expert noted that some patients have either real or perceived confidentiality concerns or a lack of trust in the health care system that serves as a significant barrier to testing. Additionally, a health systems expert stated that in some rural areas where everyone knows everyone else, it can be difficult to get anonymous testing and some patients may fear stigmatization from requesting a test at their primary care physician or local health clinic.

The experts agreed that the OraQuick in-home test appears to be accurate and that earlier HIV detection can bring patients into care earlier. This would allow them to better control their viral load with ART, which can improve health outcomes and reduce transmission rates. Patients who know their positive HIV status are also more likely to modify their behavior, which also can lower transmission rates.

Acceptance and adoption: Clinicians may recommend the home test if patients are reluctant to get confidential testing in a clinic, stated one clinical expert. That would lead to acceptance. But other experts stated that many clinicians would prefer rapid testing to still be performed in a clinical setting because counseling is available and the test may cost less. Patients are expected to prefer the privacy and convenience of home testing if the \$40 per test cost is not too high, some experts stated. Additionally, home testing may result in patients testing more frequently, one health system expert concluded.

Health care delivery infrastructure and patient management: The experts thought diffusion of the OraQuick in-home test could affect patient management in a number of ways. Patients will be presenting to clinics, concerned about a positive HIV result that needs confirmation; this could add to demands on facilities providing followup testing and HIV treatment. Additionally, patients with a positive OraQuick test result could present to clinic in anxious or suicidal states, which could have been mitigated with the counseling given before and after testing when the test is performed in a clinic, one clinical expert stated. But the number of “worried well” patients requesting rapid testing in clinics could reduce demands on facilities if patients choose instead to use the in-home test, the experts thought. Finally, an increase in the number of patients entering the system for treatment would increase costs to the system, but these costs could be offset by improved disease management and reduced transmission rates, some experts thought.

Health disparities: The experts were divided on how OraQuick would affect health disparities. Some thought the \$40 price could exclude individuals of low socioeconomic status from being tested, while providing a more convenient and anonymous option for patients with some access to health care. However, one clinical expert stated that for some patients, the \$40 test could cost less than having to interact with the health care system. Another expert noted that a home test could reduce disparities for patients in geographically isolated areas.

Malaria Intervention

RTS,S/AS01 (Mosquirix) for Prevention of Malaria Caused by *Plasmodium falciparum*

Unmet need: Globally, an estimated 219 million people were infected with malaria and 660,000 people died from the disease in 2010, despite disseminated use of vector control with insecticide-treated bed nets and indoor residual spraying combined with intermittent prophylactic pharmacotherapy.^{175,176} Travel to endemic areas (e.g., vacation, expatriation, military service) places people at risk of contact with infected mosquitoes.¹⁷⁷ Children, pregnant women, the elderly, and immunosuppressed individuals have the highest risk of mortality.^{177,178} Vaccination against malaria parasites such as *Plasmodium falciparum*, the most deadly species of malaria parasite, could reduce the incidence of malarial disease in people living in or traveling to endemic areas.^{177,179}

Intervention: RTS,S/AS01 is a vaccine designed to prevent malarial disease caused by the parasite *P. falciparum*.¹⁸⁰ The vaccine is a recombinant protein consisting of the central repeat and C terminal portions of the *P. falciparum* circumsporozoite protein fused to hepatitis B virus surface antigen, which is expressed in the yeast *Saccharomyces cerevisiae*.^{175,181} Excess hepatitis B virus surface antigen is also expressed to form the vaccine construct into virus-like particles.¹⁸¹ RTS,S/AS01 is formulated with the proprietary adjuvant, AS01, to increase immunogenicity. AS01 consists of liposomes with two immunomodulators: 3'-O-desacyl-4'-monophosphoryl lipid A (MPL) and *Quillaja saponaria* 21 (QS21). No licensed vaccines contain AS01.¹⁸⁰

The *P. falciparum* circumsporozoite protein is thought to aid the parasite in hepatocyte entry.¹⁷⁹ RTS,S/AS01-induced immune responses are thought to provide protection by preventing sporozoites from invading hepatocytes during the short window of time in which sporozoites are in circulation or by attacking liver schizonts.¹⁸² Thus, RTS,S/AS01 belongs to a class of vaccines known as pre-erythrocytic vaccines, which are intended to prevent the parasite from entering the bloodstream.

RTS,S/AS01 purportedly induces levels of anti-circumsporozoite antibodies that are much higher than those produced by repeated natural infection. However, no clear antibody threshold of protection is established.^{182,183} RTS,S/AS01 is also purported to induce strong CD4+ T-cell responses characterized by the production of inflammatory cytokines, such as interferon gamma, which could contribute to killing liver schizonts.¹⁸² Preclinical models suggested that protective synergy exists between antibody and cellular responses against malaria infection.¹⁸³

RTS,S/AS01 is theorized by some investigators to reduce the risk of infection from each exposure, rather than conferring “all or nothing” protection to those taking the vaccine. Thus, vaccinated individuals could eventually experience malaria if the transmission rate is high enough. The vaccine is expected by investigators to have a greater impact on the incidence of the first or total episodes of clinical malaria than on the overall population experiencing disease. This hypothesis is supported by the available phase III data.¹⁸⁴ RTS,S/AS01 is administered in three intramuscular injections, monthly.¹⁸⁵

Clinical trials: In a phase III, randomized, controlled, double-blind trial, children (n=6,537) aged 6–12 weeks were given three doses of RTS,S/AS01 or meningococcal serogroup C conjugate vaccine as a control. The coprimary end points were vaccine efficacy against the first or only episode of clinical malaria during the 12 months after vaccination.¹⁸⁵ Vaccine efficacy was 30.1% (95% CI, 23.6 to 36.1) against the first or only episode of clinical malaria in the intention-to-treat population up to 14 months after the first dose of vaccine. Vaccine efficacy was 31.3% (97.5% CI, 23.6 to 38.3) against clinical malaria in the per-protocol population.¹⁸⁵ RTS,S/AS01 was 26.0% (95% CI, -7.4 to 48.6) and 36.6% (95% CI, 4.6 to 57.7) effective against severe malaria in the intention-to-treat population and per-protocol populations, respectively.¹⁸⁵

Children given RTS,S/AS01 had no differences in the frequency of serious adverse events compared with children given control vaccine. Children given RTS,S/AS01 were 99.7% seropositive for anti-circumsporozoite antibodies 1 month after administration of the third dose of vaccine.¹⁸⁵

In another phase III, randomized, controlled, double-blind trial, children (n=6,000) aged 5–15 months or 6–12 weeks were given RTS,S/AS01 or a nonmalaria control vaccine. The primary end point of the analysis was vaccine efficacy against clinical malaria during the 12 months.¹⁸⁶ Vaccine efficacy against clinical malaria was 50.4% (95% CI, 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population in children aged 5–15 months, in the 14 months following the first dose of vaccine. Additionally, vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8 to 60.5) and 47.3% (95% CI, 22.4 to 64.2) in the intention-to-treat population and in the per-protocol population, respectively. When both age groups were combined, vaccine efficacy against severe malaria was 34.8% (95% CI, 16.2 to 49.2) in the per-protocol population with an average follow-up of about 11 months.

Children given RTS,S/AS01 had no differences in the frequency of serious adverse events compared with children given control vaccine. Generalized convulsive seizures were reported at a rate of 1.04 per 1,000 doses (95% CI, 0.62 to 1.64) in patients aged 5–15 months who were given RTS,S/AS01.¹⁸⁶

According to one phase II study, RTS,S/AS01 demonstrated efficacy in the first year that waned over time and with increasing malaria exposure.¹⁸⁷ Additional studies are needed to determine the level of protection conferred by RTS,S and the optimal frequency of booster immunizations required to maximize the protective effects of the vaccine.^{185,187}

Manufacturer and regulatory status: The RTS,S construct was created in 1987 by scientists working at GlaxoSmithKline, Middlesex, UK, in collaboration with the U.S. Walter Reed Army Institute of Research, Bethesda, MD.¹⁷⁹ In January 2001, GlaxoSmithKline and the PATH Malaria Vaccine Initiative (MVI), Washington, DC, with funding from the Bill & Melinda Gates Foundation to MVI, entered into a public-private partnership to develop an RTS,S-based vaccine for infants and young children living in regions endemic for malaria in sub-Saharan Africa.¹⁷⁹

RTS,S/AS01 is in phase III development with longer-term results of protective efficacy 30 months after the third dose of vaccine expected to be available by the end of 2014.¹⁸⁸ These results are expected to be the basis of filings that could lead to regulatory approval by 2015.¹⁸⁹

Although vaccines typically gain marketing approval only when they demonstrate efficacy greater than 90%, the World Health Organization has called for a first-generation malaria vaccine with 50% efficacy against serious disease by 2015, with second-generation vaccines providing at least 80% efficacy by 2025.¹⁹⁰

Diffusion: The manufacturer has pledged to sell the vaccine for 5% above the total costs of development. This margin will purportedly be used to fund additional research for tropical diseases.¹⁸⁹ Costs could be significantly higher for people in the developed world who plan to travel to endemic areas.

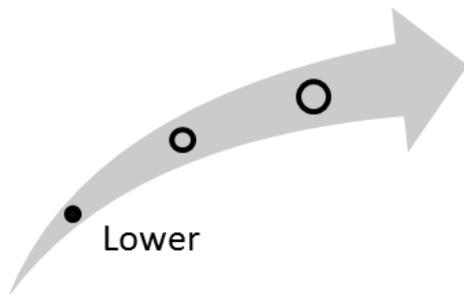
Countries endemic for malaria such as Ghana, Africa, have started to develop a walking cold chain (controlling the temperature at which the vaccine is shipped and stored) to disseminate RTS,S/AS01, if approved for marketing, in conjunction with rotavirus and pneumococcal vaccines as part of the Expanded Programme on Immunization.¹⁹¹

Clinical Pathway at Point of this intervention

Malaria prevention efforts use insecticide-treated bed nets, residual spraying, and personal mosquito repellent as well as prophylactic use of antimalarial drugs. Patients with malaria are often

treated with antimalarial agents including chloroquine, hydroxychloroquine, mefloquine, quinine sulfate, or a combination of atovaquone and proguanil.¹⁹² RTS,S/AS01 is intended to prevent the incidence of malarial disease caused by infection with *P. falciparum* and would be used in combination with current prophylactic measures.¹⁷⁸

Figure 8. Overall high-impact potential: RTS,S/AS01 (Mosquirix) for prevention of malaria caused by *Plasmodium falciparum*



Overall, experts commenting on this intervention noted a significant unmet need for protection against malarial disease for people living in or traveling to areas endemic for *P. falciparum*. The experts stated that 30% efficacy in children aged 6–12 weeks and 50% efficacy in children aged 5–17 months could significantly improve health outcomes. However, the experts noted that suboptimal efficacy and waning protection provide a need for further development of second-generation vaccines. RTS,S/AS01 is expected to reduce demands on malaria treatment facilities in endemic areas, but could require additional infrastructure investment for cold chain management and patient followup for subsequent booster immunizations. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹⁹³⁻¹⁹⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Malaria represents a serious health threat to people traveling to endemic areas for business, leisure, or military service as well as those who reside in endemic areas. Malaria treatment can be costly and lengthy; better preventative options such as vaccination are welcomed, the experts stated. Resistance to current prophylactic and treatment modalities by vector and parasite also increase the need for an effective vaccine, one research expert stated. Additionally, global climate change could present a threat of malaria resurgence in the United States, as research has shown malaria prevalence to be significantly affected by climate, one research expert stated.

A 50% reduction in clinical malaria among children and infants is a welcome advance, because the disease is so widespread in endemic areas, and vaccination could lead to a large reduction in the burden of disease and improved health outcomes, one clinical expert noted. However, the waning vaccine efficacy observed reveals the need for additional studies to determine the frequency of booster immunizations needed to maximize protective efficacy, some experts noted.

Acceptance and adoption: Clinicians are expected to widely accept a vaccine that can prevent 30% to 50% of clinical malaria caused by *P. falciparum*. Experts cited the World Health Organization's call for a malaria vaccine with 50% efficacy by 2015 and 80% efficacy by 2025 as contributing to acceptance of a vaccine with less than 90% efficacy, a typical cutoff for vaccine approval and acceptance.

Parents of children in areas endemic to malaria are expected to accept a vaccine that can reduce the risk of malarial disease. However, adult patients at moderate risk of contracting malaria may not widely accept a vaccine that has shown a 30% reduction in disease if the vaccine is not covered by insurance or is perceived as expensive, one expert with a research perspective noted.

Health care delivery infrastructure and patient management: Most experts agreed that vaccination with RTS,S/AS01 would impact health care infrastructure by reducing demands on facilities that treat malaria. Experts predict the vaccine will be administered with other childhood immunizations for pediatric patients, requiring minimal changes in patient management and infrastructure. Adults could have to make additional visits to a health care facility. Changes to current infrastructure and patient management would be needed for cold chain management and could pose a barrier to diffusion, one clinical expert noted. Additionally, the clinical expert cited the waning immunity of RTS,S/AS01 could require better management of patient records as well as increased patient visits and followup compared with current management protocols.

Health disparities: Experts agreed that the manufacturer's pledge to sell the vaccine at a cost that is projected to be 5% above the total cost of development would reduce health care disparities globally. However, experts noted that patients in developed countries are expected to pay more for the cost of developing the vaccine, which could make the vaccine expensive in developed countries due to the limited patient base in those countries.

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