Healthcare Quality Reporting Program

HOSPITAL-ACQUIRED INFECTIONS SUBCOMMITTEE

8-9am, August 18, 2014
Healthcentric Advisors, 235 Promenade Street, Suite 500

1. Welcome & today’s meeting objectives (8am)
   - Meeting chairs: L. Mermel and S. Viner-Brown
   - Program staff: R. Baier, E. Cooper
   - Others in attendance: L. Martino, S. Turner

2. Review of the previous meeting’s action items (8:05am)
   - Research CDC hand hygiene education videos and tests (Rosa/Emily) – In progress
     We have begun to identify resources, but have not completed this action item pending endorsement from Dr. Fine and the Steering Committee.

   - Discuss hand hygiene recommendations with the Steering Committee (Rosa/Emily/Sam) – Complete
     We brought the recommendations to the Steering Committee and communicated them separately to Dr. Fine, who was unable to attend that meeting.

3. Hand hygiene standards (8:10am)
   - Review discussion with Steering Committee
     - The Steering Committee expressed support for the Subcommittee’s recommendations, with most discussion focusing on an educational program for LIPs.
     - However, Dr. Fine was concerned that educational programs put too much of the responsibility on the individuals, and do not hold the facilities accountable. He requested additional information about CDC and Joint Commission measurement standards, etc., prompting today’s follow-up discussion.

   - Discussion themes included:
     - The three possible strategies for measurement: product use, survey, surveillance by direct observation or electronically.
     - The possible gap between the standardized measurement envisioned by Dr. Fine and meaningful, comparable statewide measurement, given logistical and operational constraints.
     - Implementation of policies for LIPs who are non-compliant or repeat non-compliant, such as noting hand hygiene compliance on annual evaluations.
     - Increasing consumer awareness of importance of hand hygiene.
The group recommended that Dr. Mermel meet directly with Dr. Fine to provide additional detail and nuance for the Subcommittee’s previous recommendations.

- Suggested reading: Joint Commission and WHO guidelines (no handouts)

4. Project to improve consumer awareness of HAI reports (8:25am)

- Rosa and Emily provided an overview of a quality improvement project to improve consumer awareness of the available reports published by this program.
- Rosa asked for suggestions about how to market the reports, e.g., via stakeholder and consumer groups who could act as a conduit to the consumer population.
- We will be measuring the success of this project by monitoring traffic to the program’s HAI pages on the Department of Health website.

5. Program updates (8:40am)

- Flu data and reporting (handout)
  - Rosa reviewed the preliminary data available from the Immunizations Program.
  - The Immunizations Program is now planning to publish these data. We will wait until we see their public-facing reports before creating ours, in order to avoid duplicating efforts.

- Senator Whitehouse’s upcoming meeting
  - This group previously provided input on Healthcentric Advisors’ response to Senator Whitehouse’s ideas for HAI legislation.
  - As follow-up, the Senator is hosting a meeting to discuss updated legislative ideas. His team invited representatives from this committee and the taskforce (below), among others, and we will provide an update at the next meeting.

6. Update: HEALTH Taskforce for Antimicrobial Stewardship and Environmental Control (8:50am)

- In response to our 51/51 ranking in C. difficile LabID events on Hospital Compare, Dr. Fine convened a taskforce. Len provided a brief update; Nicole will provide additional detail in October.
- This group is providing recommendations to HEALTH re: antimicrobial stewardship and environmental cleaning in hospitals and long-term care facilities. They are drafting a letter to Dr. Fine, which we will be able to share with this group in October.

7. Action Items (8:55am)

- Share WHO Technical Manual with the committee (Emily)
- Schedule meeting between Dr. Mermel and Dr. Fine (Sam)
- Research electronic hand hygiene measurement tools (Emily/Rosa)
- Perform environmental scan re: hand hygiene reporting (Emily/Rosa)
- Share taskforce’s letter to Dr. Fine with the committee (Nicole/Rosa)

Next Meeting: October 20, 2014
Healthcare Quality Reporting Program

EMPLOYEE INFLUENZA (FLU) VACCINATION STATUS
Preliminary Data

% of Hospital HCWs Vaccinated, by Flu Season
(100% response rate from hospitals)

% of Hospital HCWs Vaccinated - Current & Most Recent Flu Seasons
(100% response rate from hospitals)

Bradley Hospital
Butler Hospital
Eleanor Slater Hospital
Kent County Memorial Hospital
Landmark Medical Center
Memorial Hospital of Rhode...
Newport Hospital
Our Lady of Fatima
Rhode Island Hospital
Roger Williams Medical Center
South County Hospital
The Miriam Hospital
Westerly Hospital
Women & Infants Hospital of RI
Healthcare Quality Reporting Program
EMPLOYEE INFLUENZA VACCINATION STATUS
Preliminary Data

Nursing Home Data Submission Response Rate, by Flu Season

% of Nursing Home HCWs Vaccinated, by Flu Season

Hanna Kim, PhD; Megan C. Lindley, MPH; Donna Dube, MS, RN; Elizabeth J. Kalayil, MPH; Kristi A. Paiva, MPH; Patricia Raymond, RN, MPH

Context: In October 2012, the Rhode Island Department of Health (HEALTH) amended its health care worker (HCW) vaccination regulations to require all HCWs to receive annual influenza vaccination or wear a surgical mask during direct patient contact when influenza is widespread. Unvaccinated HCWs failing to wear a mask are subject to a fine and disciplinary action. Objective: To describe the implementation of the 2012 Rhode Island HCW influenza vaccination regulations and examine their impact on vaccination coverage. Design: Two data sources were used: (1) a survey of all health care facilities subject to the HCW regulations and (2) HCW influenza vaccination coverage data reported to HEALTH by health care facilities. Descriptive statistics and paired t tests were performed using SAS Release 9.2. Setting and participants: For the 2012-2013 influenza season, 271 inpatient and outpatient health care facilities in Rhode Island were subject to the HCW regulations. Main Outcome Measure: Increase in HCW influenza vaccination coverage. Results: Of the 271 facilities, 117 facilities completed the survey (43.2%) and 160 facilities reported vaccination data to HEALTH by health care facilities. The majority of facilities perceived benefits to collecting HCW influenza vaccination data, including strengthening infection prevention efforts (83.2%) and improving patient and coworker safety (75.2%). Concurrent with the new regulations, influenza vaccination coverage among employee HCWs in Rhode Island increased from 69.7% in the 2011-2012 influenza season to 87.2% in the 2012-2013 season. Conclusion: Rhode Island’s experience demonstrates that statewide HCW influenza vaccination requirements incorporating mask wearing and moderate penalties for noncompliance can be effective in improving influenza vaccination coverage among HCWs.

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The authors thank Tricia Washburn, Denise Cappelli, Joseph Wendelken, and Angela Such of the Rhode Island Department of Health for their assistance in completing the evaluation, and the health care facility staff who participated in the evaluation survey for providing their facilities’ experience in implementing the HCW regulations.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Rhode Island Department of Health.

The authors and/or their significant others have no financial interests to disclose.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal’s Web site (http://www.JPHMP.com).

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DOI: 10.1097/PHH.0000000000000128
KEY WORDS: evaluation, health care worker (HCW), regulations, influenza vaccination

Since 1984, the Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices has recommended annual seasonal influenza vaccination for health care workers (HCWs).\(^1,2\) Vaccinating HCWs against influenza can reduce influenza illness, staff absenteeism, transmission of influenza, and influenza-related morbidity and mortality among patients in health care settings.\(^3,9\) Despite the documented benefits and Advisory Committee on Immunization Practices’ long-standing recommendations, the overall influenza vaccination rate for HCWs has remained below the Healthy People 2020 target of 90% nationally.\(^10\) With the notion that voluntary programs are insufficient to increase HCW influenza vaccination rates to the targeted levels, mandatory vaccination programs have been recently endorsed by many professional societies, state health departments, and other public health advocacy organizations.\(^11-13\) Mandatory vaccination programs have successfully increased influenza vaccination coverage among HCWs in a variety of health care settings.\(^10,14-17\)

In 2007, the Rhode Island Department of Health (HEALTH) required all health care facilities to offer influenza vaccine at no cost to their workers, provide education on influenza illness and the safety of influenza vaccine, and report HCW influenza vaccination coverage to HEALTH.\(^18\) Despite these requirements, influenza vaccination coverage for HCWs in Rhode Island increased only marginally for several years, reaching less than 70% in the 2011-2012 influenza season (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2012).

In October 2012, to further increase influenza vaccination coverage among HCWs, HEALTH amended the 2007 regulations to include stricter requirements for HCWs who choose to remain unvaccinated (referred to here as “the HCW regulations”).\(^19\) The amended regulations require all HCWs to either receive influenza vaccination or provide a proof of medical exemption or a declination statement to their health care facilities by December 15th of each year. Unvaccinated workers in facilities must wear a surgical face mask during direct, face-to-face contact with patients when influenza is declared widespread. Unvaccinated HCWs who fail to comply with the mask-wearing requirement are subject to a $100 fine for each violation and possible disciplinary action by their licensing board.\(^19\) In the regulations, a HCW is defined as any person who is temporarily or permanently employed or serves as a volunteer in a health care facility and who has or may have direct contact with a patient in the facility. A health care facility is defined as any institutional health service provider or facility that is licensed by HEALTH, including but not limited to hospitals, nursing homes, home care providers, home nursing care providers, kidney disease treatment centers, and hospice providers.\(^19\)

The HCW regulations became effective on October 25, 2012, as the 2012-2013 influenza season was starting; influenza was declared widespread in Rhode Island on December 5, 2012.\(^20\) To assess effectiveness of the new mandatory vaccination regulations, HEALTH conducted both qualitative and quantitative evaluations in collaboration with CDC. This report presents results of the quantitative evaluation; the qualitative evaluation is presented elsewhere.\(^21\) This evaluation examined (1) the processes/methods used by health care facilities to implement the HCW regulations and (2) the impact of the regulations on HCW influenza vaccination coverage during the 2012-2013 influenza season.

Methods

Data

Data were analyzed from 2 sources: (1) an evaluation survey of health care facilities conducted by HEALTH (facility evaluation survey) and (2) HCW influenza vaccination data reported to HEALTH by health care facilities (HCW influenza vaccination report).

Facility evaluation survey

The survey was conducted to evaluate how health care facilities implemented the HCW regulations during the 2012-2013 influenza season. The target of the evaluation survey was all health care facilities subject to the HCW regulations for the 2012-2013 influenza season (n = 271). A comprehensive list of facilities was obtained from HEALTH’s Office of Facility Regulation. HEALTH identified a contact person considered most appropriate to respond to the survey in each facility, usually the person who reported HCW influenza vaccination data to HEALTH. A link to the survey was e-mailed to the contact person with a letter from the director of HEALTH, requesting his or her participation in the survey. The survey data were collected from August 19 to September 12, 2013, through HEALTH’s Web-based survey system.

HCW influenza vaccination report

The aggregate counts of HCW influenza vaccination status reported by health care facilities to HEALTH were used to estimate vaccination coverage. The elements of data reporting include HCW influenza vaccination status (vaccinated, medical exemption,
declination, and unknown status) for employees, nonemployee licensed independent practitioners (LIP), and nonemployee adult students/trainees/volunteers (STV). These elements were adapted from the National Healthcare Safety Network’s Healthcare Personnel Influenza Vaccination Summary Measure. The 2012-2013 influenza season data were compared with those of the 2011-2012 influenza season when the data could be compared.

● Results

Of the 271 facilities subject to the HCW regulations, 137 (50.6%) responded to evaluation survey. Twenty facilities that answered only demographic questions were excluded from analyses, leaving a final analytic number of 117 facilities (43.2%). Of the 117 facilities, about half (49.1%) had an employee size of 100 or less, and almost all facilities (97.3%) reported HCW influenza vaccination data to HEALTH during the 2012-2013 influenza season (see Supplemental Digital Content 1 Table, available at http://links.lww.com/JPHMP/A101, which describes the characteristics of facilities responding to evaluation survey).

Facility’s implementation of HCW regulations

The first 3 items in Table 1 measure how health care facilities implemented the HCW regulations. Although almost all facilities responding to the survey (96.6%) applied HCW regulations on vaccination and masking to their employees, fewer facilities applied the regulations to their nonemployees.

During widespread influenza, facilities required mask wearing for unvaccinated HCWs under different circumstances. Nearly two-fifths of facilities (39.7%) required mask wearing any time the HCW might have face-to-face patient contact (including at registration), and one-third of facilities (33.6%) required it any time the HCW was in a patient care area/patient care unit. Twelve percent required masking only when the HCW was providing clinical care (ie, within 6 ft of a patient), and 11.2% required it any time the HCW was inside any part of the facility.

The majority of facilities reported that the supervisors of HCWs were responsible for verifying mask compliance (69.9%), and more than one-half of facilities (56.6%) reported that each unvaccinated HCW was responsible for wearing his or her mask.

Perceived benefits of collecting data on HCW influenza vaccination

The last item in Table 1 presents perceived benefits of collecting HCW influenza vaccination data. The most
| Facility’s Implementation of HCW Regulations and Perceived Benefits of Collecting HCW Influenza Vaccination Data, Overall and by Facility Size, 2012-2013 Influenza Seasona |
|---|---|---|---|
| | All Facilities, n (%) | Small Facilities, n (%) | Large Facilities, n (%) |
| To which of the following groups did this facility apply the new HCW regulations on vaccination and masking of HCWs?c | | | |
| Employees | 113 (96.6) | 53 (93.0) | 59 (100.0) | <.05 |
| Nonemployees (licensed independent practitioners) | 78 (66.7) | 30 (52.6) | 47 (79.7) | <.01 |
| Nonemployees (adult students and trainees) | 60 (51.3) | 19 (33.3) | 40 (67.8) | <.01 |
| Nonemployees (adult volunteers) | 62 (53.0) | 14 (24.6) | 47 (79.7) | <.01 |
| During widespread influenza, under what circumstances were unvaccinated HCWs at this facility required to wear masks? | | | |
| Any time the HCW was inside any part of the facility | 13 (11.2) | 7 (12.5) | 6 (10.2) | NS |
| Any time the HCW was in a patient care area/patient care unit | 39 (33.6) | 15 (26.8) | 24 (40.7) | |
| Any time the HCW might have face-to-face patient contact (including at registration) | 46 (39.7) | 23 (41.1) | 22 (37.3) | |
| Only when the HCW was providing clinical care (ie, within 6 ft of a patient) | 14 (12.1) | 8 (14.3) | 6 (10.2) | |
| Not applicable: all HCWs in this facility received influenza vaccination | 2 (1.7) | 1 (1.8) | 1 (1.7) | |
| Not applicable: unvaccinated HCWs in this facility did not have to wear a mask | 2 (1.7) | 2 (3.6) | 0 (0.0) | |
| How did this facility make sure that unvaccinated HCWs were wearing masks when required?c | | | |
| Each unvaccinated HCW was responsible for wearing his or her mask | 64 (56.6) | 31 (56.4) | 33 (57.9) | NS |
| Peers/coworkers of HCWs were responsible for verifying mask compliance | 18 (15.9) | 6 (10.9) | 12 (21.1) | NS |
| Supervisors of HCWs were responsible for verifying mask compliance | 79 (69.9) | 34 (61.8) | 44 (77.2) | NS |
| Checked identification badge for quick verification of vaccination | 19 (16.8) | 6 (10.9) | 13 (22.8) | NS |
| Not applicable: unvaccinated HCWs in this facility did not have to wear a mask | 2 (1.2) | 2 (3.6) | 0 (0.0) | NS |
| What do you believe are the benefits of collecting data on influenza vaccination of HCWs in this facility?c | | | |
| Helps increase vaccination promotion efforts at facility | 80 (70.8) | 32 (58.2) | 47 (82.5) | <.01 |
| Helps improve HCW tracking system | 65 (57.5) | 31 (56.4) | 34 (59.6) | NS |
| Provides data for The Joint Commission reporting requirements | 37 (32.7) | 11 (20.0) | 26 (45.6) | <.01 |
| Provides data for health care facility administration/system reporting requirements | 71 (62.8) | 30 (54.5) | 41 (71.9) | NS |
| Strengthens infection prevention efforts | 94 (83.2) | 41 (74.5) | 52 (91.2) | <.05 |
| Helps improve patient and coworker safety | 85 (75.2) | 43 (78.2) | 42 (73.7) | NS |
| Communicates vaccination rates to HCWs at facility | 50 (44.2) | 15 (27.3) | 35 (61.4) | <.01 |
| No benefit | 4 (3.5) | 3 (5.5) | 1 (1.8) | NS |

Abbreviations: HCW indicates health care worker; NS, not significant.

*aFrom Facility Evaluation Survey conducted by HEALTH during August 19 to September 12, 2013.

bP values are from the $\chi^2$ test; $P < .05$ is presented in bold.

cEach response category is treated as a separate question.
frequently reported benefits were that it strengthens infection prevention efforts (83.2%), helps improve patient and coworker safety (75.2%), and helps increase vaccination promotion efforts at the facility (70.8%). Respondents from large facilities were more likely to report benefits of collecting data than respondents from small facilities for several aspects: collecting data helps increase vaccination promotion efforts at the facility; it helps provide data for The Joint Commission reporting requirements; it strengthens infection prevention efforts; and it helps communicate vaccination rates to HCWs at the facility.

Facility's policy on HCW influenza vaccination

The first item in Table 2 presents facilities' policy on HCW influenza vaccination. Between the 2011-2012 influenza season (before new regulations) and the 2012-2013 influenza season (after new regulations), the proportion of facilities requiring unvaccinated HCWs to wear a mask during patient care activities increased dramatically from 9.4% to 94.0% (P < .01). The increase was observed in both small and large facilities. In the 2012-2013 influenza season, compared with prior season, more facilities required HCWs who declined vaccination to undergo additional education on influenza disease and vaccination (23.9% vs 43.6%; P < .01), required them to meet with a disciplinary committee or a supervisor (3.4% vs 20.5%; P < .01), did not permit them to work at the facilities (5.1% vs 16.2%; P < .01), and assigned them to different units or job duties during widespread influenza (0% vs 6.8%; P < .01).

Although the proportion of facilities allowing medical exemptions remained similar between the 2 influenza seasons, fewer facilities allowed religious or personal belief exemptions in the 2012-2013 influenza season (38.5%), compared with the 2011-2012 influenza season (50.4%).

HCW influenza vaccination promotion strategies

The last item in Table 2 shows strategies used to encourage HCWs to receive the influenza vaccine. Overall, of the 11 promotion strategies reviewed, only 1 strategy was used by more facilities following implementation of the new regulations: the percentage of facilities providing education to staff who reported that they were challenged by the facility’s influenza vaccination policy increased significantly from 34.5% in the 2011-2012 influenza season to 65.5% in the 2012-2013 influenza season (P < .01). Although the percentages increased significantly in both small and large facilities, the amount of increase was greater in large facilities (38.6 percentage points) than in small facilities (23.6 percentage points).

For small facilities, many vaccination promotion strategies were less likely to be used in the 2012-2013 influenza season than in the 2011-2012 flu season. Fewer small facilities provided free vaccination to HCWs (83.6%-67.3%; P < .05); used mobile vaccination carts (10.9%-1.8%; P < .05); provided vaccination in wards, clinics, cafeterias, or common areas (34.5%-23.6%; P < .05); provided vaccination during nights and weekends (38.2%-23.6%; P < .05); provided visible vaccination of key personnel (38.2%-25.5%; P < .05); and provided education on the benefits and risks of vaccination (83.6%-65.5%; P < .01). However, use of those strategies did not change significantly in large facilities between the 2011-2012 and 2012-2013 influenza seasons.

HCW influenza vaccination coverage

Of the 271 facilities subject to the HCW regulations, 160 facilities (59.0%) reported their HCW influenza vaccination data to HEALTH in the 2012-2013 influenza season (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2013), a notable increase from 73 facilities (26.9%) in the 2011-2012 influenza season (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2012). The Figure shows that of the 160 facilities, all reported having 1 or more employee HCWs in their facility, 105 facilities (65.6%) reported having 1 or more nonemployee LIP, and 80 facilities (50.0%) reported having 1 or more nonemployee STV during the influenza season (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2013).

The proportion of HCWs who received influenza vaccination varied by HCW type: 87.2% of employee HCWs, 81.6% of nonemployee LIPs, and 56.1% of nonemployee STVs were vaccinated. The large coverage differences among HCW types were mainly due to differences in the proportion of unknown vaccination status of each group. Whereas only 2.1% of employee HCWs had unknown vaccination status, 14.6% of LIPs and 40.0% of STVs had unknown status.

Overall, influenza vaccination coverage among employee HCWs in Rhode Island increased from 69.7% in the 2011-2012 influenza season to 87.2% in the 2012-2013 influenza season. Specifically, vaccination coverage for employee HCWs increased from 74% to 88.6% in hospitals, from 60% to 90.6% in nursing homes, and 55% to 71.2% in home nursing care providers (data not shown) (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2012; State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2013). However, due to large missing data of nonemployee HCWs,
<table>
<thead>
<tr>
<th>Facility policy for HCW influenza vaccination</th>
<th>2011-2012 Season, n (%)</th>
<th>2012-2013 Season, n (%)</th>
<th>( P^b )</th>
<th>By Facility Size</th>
<th>2011-2012 Season, n (%)</th>
<th>2012-2013 Season, n (%)</th>
<th>( P^b )</th>
<th>2011-2012 Season, n (%)</th>
<th>2012-2013 Season, n (%)</th>
<th>( P^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated HCWs are required to wear a mask during patient care activities when influenza is widespread</td>
<td>11 (9.4)</td>
<td>110 (94.0)</td>
<td>&lt;.01</td>
<td>Small Facilities</td>
<td>8 (14.0)</td>
<td>51 (89.5)</td>
<td>&lt;.01</td>
<td>3 (5.1)</td>
<td>58 (98.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HCWs who decline vaccination are required to undergo additional education on influenza disease and vaccination</td>
<td>28 (23.9)</td>
<td>51 (43.6)</td>
<td>&lt;.01</td>
<td>Large Facilities</td>
<td>15 (26.3)</td>
<td>21 (36.8)</td>
<td>NS</td>
<td>13 (22.0)</td>
<td>30 (50.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HCWs who decline vaccination are required to meet with a disciplinary committee or a supervisor</td>
<td>4 (3.4)</td>
<td>24 (20.5)</td>
<td>&lt;.01</td>
<td></td>
<td>4 (7.0)</td>
<td>14 (24.6)</td>
<td>&lt;.05</td>
<td>0 (0.0)</td>
<td>10 (16.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HCWs who decline vaccination and do not have an exemption are not permitted to work at the facility</td>
<td>6 (5.1)</td>
<td>19 (16.2)</td>
<td>&lt;.01</td>
<td></td>
<td>3 (5.3)</td>
<td>11 (19.3)</td>
<td>&lt;.05</td>
<td>3 (5.1)</td>
<td>8 (13.6)</td>
<td>NS</td>
</tr>
<tr>
<td>HCWs who decline vaccination are assigned to different units or job duties during periods of widespread influenza</td>
<td>0 (0.0)</td>
<td>8 (6.8)</td>
<td>&lt;.01</td>
<td></td>
<td>0 (0.0)</td>
<td>6 (10.5)</td>
<td>&lt;.05</td>
<td>0 (0.0)</td>
<td>2 (3.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Medical exemptions to vaccination are allowed</td>
<td>81 (69.2)</td>
<td>82 (70.1)</td>
<td>NS</td>
<td></td>
<td>34 (59.6)</td>
<td>31 (54.4)</td>
<td>NS</td>
<td>46 (78.0)</td>
<td>50 (84.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Religious or personal belief exemptions to vaccination are allowed</td>
<td>59 (50.4)</td>
<td>45 (38.5)</td>
<td>&lt;.05</td>
<td></td>
<td>24 (42.1)</td>
<td>21 (36.8)</td>
<td>NS</td>
<td>34 (57.6)</td>
<td>23 (39.0)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Facility does not have a formal influenza vaccination policy for HCWs</td>
<td>6 (5.1)</td>
<td>6 (5.1)</td>
<td>NS</td>
<td></td>
<td>4 (7.0)</td>
<td>5 (8.8)</td>
<td>NS</td>
<td>1 (1.7)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Strategies used to encourage HCWs to receive the influenza vaccine</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide free vaccination to HCWs</td>
<td>96 (85.0)</td>
<td>87 (77.0)</td>
<td>NS</td>
<td></td>
<td>46 (83.6)</td>
<td>37 (67.3)</td>
<td>&lt;.05</td>
<td>49 (86.0)</td>
<td>49 (86.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Use mobile vaccination carts</td>
<td>32 (28.3)</td>
<td>26 (23.0)</td>
<td>NS</td>
<td></td>
<td>6 (10.9)</td>
<td>1 (1.8)</td>
<td>&lt;.05</td>
<td>26 (45.6)</td>
<td>25 (43.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide vaccination in wards, clinics, cafeterias, or common areas (eg, teams of qualified persons administered vaccinations)</td>
<td>56 (49.6)</td>
<td>53 (46.9)</td>
<td>NS</td>
<td></td>
<td>19 (34.5)</td>
<td>13 (23.6)</td>
<td>&lt;.05</td>
<td>36 (63.2)</td>
<td>39 (68.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide vaccination during nights and weekends</td>
<td>57 (50.4)</td>
<td>52 (46.0)</td>
<td>NS</td>
<td></td>
<td>21 (38.2)</td>
<td>13 (23.6)</td>
<td>&lt;.05</td>
<td>36 (63.2)</td>
<td>39 (68.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide vaccination at any meetings (grand rounds, in-service, staff meetings, etc)</td>
<td>41 (36.3)</td>
<td>36 (31.9)</td>
<td>NS</td>
<td></td>
<td>16 (29.1)</td>
<td>11 (20.0)</td>
<td>NS</td>
<td>25 (43.9)</td>
<td>25 (43.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide visible vaccination of key personnel</td>
<td>46 (40.7)</td>
<td>39 (34.5)</td>
<td>NS</td>
<td></td>
<td>21 (38.2)</td>
<td>14 (25.5)</td>
<td>&lt;.05</td>
<td>25 (43.9)</td>
<td>25 (43.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide education on the benefits and risks of vaccination</td>
<td>97 (85.8)</td>
<td>88 (77.9)</td>
<td>NS</td>
<td></td>
<td>46 (83.6)</td>
<td>36 (65.5)</td>
<td>&lt;.01</td>
<td>50 (87.7)</td>
<td>51 (89.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide education to staff who believed that they were challenged by the new policy</td>
<td>39 (34.5)</td>
<td>74 (65.5)</td>
<td>&lt;.01</td>
<td></td>
<td>19 (34.5)</td>
<td>32 (58.2)</td>
<td>&lt;.01</td>
<td>20 (35.1)</td>
<td>42 (73.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Track unit- or department-specific vaccination rates for some areas</td>
<td>38 (33.6)</td>
<td>32 (28.3)</td>
<td>NS</td>
<td></td>
<td>10 (18.2)</td>
<td>5 (8.1)</td>
<td>NS</td>
<td>28 (49.1)</td>
<td>27 (47.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide feedback of vaccination rates to facility administration</td>
<td>73 (64.6)</td>
<td>66 (58.4)</td>
<td>NS</td>
<td></td>
<td>30 (54.5)</td>
<td>23 (41.8)</td>
<td>NS</td>
<td>43 (75.4)</td>
<td>43 (75.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Provide incentives for vaccination (candy, entry into raffle or prize drawing, time off, etc)</td>
<td>21 (18.6)</td>
<td>23 (20.4)</td>
<td>NS</td>
<td></td>
<td>5 (9.1)</td>
<td>4 (7.3)</td>
<td>NS</td>
<td>16 (28.1)</td>
<td>19 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td>None of the above</td>
<td>1 (0.9)</td>
<td>2 (1.8)</td>
<td>NS</td>
<td></td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td>NS</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: HCW indicates health care worker; NS, not significant.

aFrom Facility Evaluation Survey conducted by HEALTH during August 19 to September 12, 2013.

bP values are from the paired \( t \) test (before and after); \( P < .05 \) is presented in bold.

cEach response category is treated as a separate question.
vaccination coverage for LIPs and STVs could not be accurately compared between the 2 influenza seasons.

● Discussion

To our knowledge, Rhode Island is the first US state to mandate comprehensive, statewide annual influenza vaccination for HCWs. 27-29 Fifteen other states have enacted laws pertaining to HCW influenza vaccination administration, but the laws vary in their scope and types of health care settings covered. 30 Most states apply the laws to only certain health care settings or HCW types (eg, only hospitals or only employee HCWs) or have permissive laws that do not impose strict penalties for noncompliance. 30-34 Currently, Colorado and New York have state laws requiring unvaccinated HCWs to wear surgical masks, 30 but neither of these laws predated Rhode Island’s law. In addition to the masking requirement, the Rhode Island regulations specify that “Unvaccinated HCWs who violate the masking requirement are subject to a $100 fine per violation and disciplinary action. The $100 fine is not payable to the facility. It will be levied only after a complaint is filed with HEALTH, investigated, referred to the appropriate licensing board, and after an opportunity for a hearing. If the fine is levied, it will be payable to the General Treasurer.” 19,35 However, in the 2012-2013 influenza season, no complaints were filed with HEALTH, and no fines were collected.

The most successful outcome of the HCW regulations in Rhode Island was that overall influenza vaccination coverage for employee HCWs increased 17.5 percentage points among reporting facilities, from 69.7% in the 2011-2012 influenza season to 87.2% in the 2012-2013 influenza season (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2012; State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2013). Although vaccination coverage increased in all types of health care settings, the coverage increased particularly among HCWs in nursing homes, where influenza vaccination coverage had been traditionally low in Rhode Island as well as nationally (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2012). 10 Rhode Island achieved more than 90% coverage among employee HCWs at reporting nursing homes during the 2012-2013 influenza season (State of Rhode Island and Providence Plantations Department of Health, unpublished data, 2013). Since nursing homes are regularly inspected and assessed by HEALTH, the new regulations may have increased the facilities’ awareness of the importance of HCW influenza vaccination. For hospitals, the vaccination coverage in Rhode Island also increased significantly after enacting the HCW regulations, although the magnitude of increase was somewhat smaller than for nursing homes. These results are contrasted with the experience of California’s 2006 influenza vaccination requirements for hospital-based HCWs, which did not increase influenza vaccination uptake. 34,36 The different outcomes may be due to differences in the regulations: while Rhode Island regulations require unvaccinated HCWs to submit signed declination statements and to wear masks during periods of widespread influenza, 19 California law requires only signed declination statements for unvaccinated HCWs. 34,36 In addition, Rhode Island regulations include specific penalties for noncompliance, which are absent in California’s law. 19,34,36

The most noticeable change between the 2011-2012 and the 2012-2013 influenza seasons was the increase in the number of facilities having a masking policy for unvaccinated HCWs. This is possibly due to the fact that facilities are required by the regulations to have masking policies in place and enforce them when influenza is declared widespread. However, the enforcement of masking among unvaccinated HCWs was identified as a major barrier for facilities to implement the HCW regulations, because it “required timely tracking of vaccination status and additional time and effort from supervisors.” 21 To better implement masking requirements in the future, it is recommended that all facility administrators clearly communicate the masking requirement to their HCWs while requiring them to receive vaccination by December 15.

It is interesting to note that most strategies promoting influenza vaccination among HCWs 35 were less likely to be used in the 2012-2013 influenza season.
than in the 2011-2012 influenza season, particularly in smaller facilities. A similar pattern was found in California after enacting the influenza vaccination requirements for hospital personnel: California hospital-based HCWs were less likely than HCWs in states without vaccination requirements to report employer policies to promote vaccination using incentives and rewards. As suggested by California’s experience, by focusing on compliance with the requirements, such as data collection and tracking, reporting, masking, and education, small facilities might have unintentionally reduced their efforts to implement other voluntary promotion strategies.

There are several limitations to this study. Only 43.2% of facilities completed the evaluation survey, and nearly all respondents reported HCW vaccination data to HEALTH. Therefore, results may not describe the experience of nonreporting facilities and may not be generalizable to all facilities in Rhode Island. Since evaluation survey data could not be linked to reported vaccination coverage because of the anonymity of the survey, relationships between vaccination coverage levels and facility policies/promotion strategies could not be examined. Data on vaccination coverage and survey information used for this study were all self-reported and not verified by HEALTH. While data regarding employee HCW influenza vaccination status were highly complete and accurate, data on nonemployee HCWs had a large proportion of unknown status, which is also reported in a national study.

Although HEALTH worked meticulously with health care facilities well in advance to prepare for implementing the HCW regulations, not all facilities submitted their HCW influenza vaccination summary data to HEALTH. Failure to report could be due to confusion on which facilities were covered by the regulations, inability to enforce requirements, and lack of resources in HEALTH to reach out to all facilities individually. For future years, HEALTH plans to clarify the definition of reporting elements, strengthen the facilities’ reporting obligations, and follow up with nonreporting facilities. In conclusion, although Rhode Island’s first-year experience of implementation of the regulations was not perfect, our data demonstrate that statewide HCW influenza vaccination requirements incorporating mask wearing and moderate penalties for noncompliance may be effective in improving influenza vaccination coverage among HCWs.

REFERENCES


Appropriate Use of Medical Resources

Antimicrobial Stewardship Toolkit
Over the past two decades, the past five years in particular, a national discussion emerged concerning the increased cost of health care. Perhaps of greater importance, increased health care costs have not always led to improved outcomes. In fact, over-diagnosis, overuse of treatments and a “try everything” approach have contributed to increased health care costs with little discernible improvement in health. At the same time, medical knowledge has increased exponentially and clinical knowledge is doubling as fast as every two years. But with all this knowledge looms a larger debate, when are we doing too much and how do we decide?

Care providers endeavor to provide the most appropriate care to patients regardless of cost, but all too often there isn’t enough discussion with patients about what is appropriate. Further, how can the health care system equip patients to participate in those discussions and make the most informed decision in partnership with their caregivers? As medical societies, provider organizations and others look for ways to drive appropriate use, hospitals and health systems can play an important role in supporting and guiding these efforts.

In 2013, the AHA, with guidance from its Committee on Clinical Leadership, examined the issue and developed the white paper Appropriate Use of Medical Resources, which identifies the drivers of health care utilization and recommends a way to move forward to reduce non-beneficial services and improve care. Among its efforts, the AHA developed a “top five” list of hospital-based procedures or interventions that should be reviewed and discussed by a patient and physician prior to proceeding, including:

• Appropriate blood management in inpatient services;
• Appropriate antimicrobial stewardship;
• Reducing inpatient admissions for ambulatory-sensitive conditions (e.g. low back pain, asthma, uncomplicated pneumonia);
• Appropriate use of elective percutaneous coronary intervention; and
• Appropriate use of the intensive care unit for imminently terminal illness (including encouraging early intervention and discussion about priorities for medical care in the context of progressive disease).

To begin the discussion, the AHA released in November 2013 the Appropriate Use of Medical Resources. We encouraged our members to share it with their board, medical staff, and community leaders and use the accompanying discussion guide to explore the issue together.

To further support hospitals’ efforts, the AHA’s Physician Leadership Forum is releasing toolkits on each of the five areas. This second toolkit focuses on antimicrobial stewardship. To access all toolkits, please visit www.aha.org/appropriateuse.

FOR MORE INFORMATION
Visit www.aha.org/appropriateuse.

CONTACT INFORMATION
Elisa Arespacochaga, director, Physician Leadership Forum, elisa@aha.org or 312-422-3329.
Antimicrobial Stewardship Toolkit

To access the toolkit, visit www.aha.org/appropriateuse.
Developed with resources from:
Association for Professionals in Infection Control and Epidemiology (APIC)
American Society of Health-System Pharmacists (ASHP)
Centers for Disease Control and Prevention (CDC)
Infectious Diseases Society of America (IDSA)
Pediatric Infectious Diseases Society (PIDS)
Society for Healthcare Epidemiology of America (SHEA)
Society of Hospital Medicine (SHM)

User Guide
The toolkit is composed of three sections:

Hospital and Health System Resources - includes a readiness assessment tool, the starting point in developing or enhancing a successful Antimicrobial Stewardship Program (ASP). The tool, a checklist developed by the CDC, should be shared with senior management, a senior leader for quality, purchasing directors, clinic managers, nurse managers, key physician leaders, risk managers, pharmacy leaders, infection preventionists and hospital epidemiologists, laboratory staff and information technology staff. For ease of use, it is divided into two sections, one for those just beginning a program, the other for those who wish to enhance an existing program.

Clinician Resources - includes webinars, clinical evidence supporting appropriate use of antibiotics, implementation guides and related articles.

Patient Resources - includes frequently asked questions, pamphlets and handouts on how patients can best engage in their care and resources on appropriate use of antibiotics.

The CDC Assessment Tool
This checklist will assist hospitals in assessing key elements needed for creating a program that ensures optimal antibiotic prescribing and appropriate use. The key elements of a successful ASP include leadership commitment, accountability, drug expertise, action, tracking, reporting and education. To access the checklist, go to http://bit.ly/1pgmuw4.

Hospital and Health System Resources
GETTING STARTED

CDC Core Elements of Hospital Antibiotic Stewardship Programs
This document summarizes core elements of successful hospital ASPs. It complements existing guidelines on ASPs from organizations including the IDSA in conjunction with SHEA, ASHP and The Joint Commission. Experience demonstrates that ASPs can be implemented effectively in a wide variety of hospitals and health systems and that success is dependent on defined leadership and a coordinated multidisciplinary approach. To download, go to http://bit.ly/1mkf6MJ.

Antibiotic Rx in Hospitals: Proceed with Caution
This fact sheet from CDC illustrates how antibiotics save lives, but poor prescribing practices put patients at unnecessary risk for preventable allergic reactions, super-resistant infections and deadly diarrhea. Errors in prescribing decisions also contribute to antibiotic resistance, making these drugs less likely to work in the future. To download, go to http://bit.ly/1iuBhQY.
ASHP Statement on the Pharmacist’s Role in Antimicrobial Stewardship and Infection Prevention and Control
Pharmacists have a responsibility to take prominent roles in ASPs and participate in the infection prevention and control programs of hospitals and health systems. Pharmacists’ responsibilities for antimicrobial stewardship and infection prevention and control include promoting the optimal use of antimicrobial agents, reducing the transmission of infections and educating health professionals, patients and the public. To download, go to http://bit.ly/1qHxaDu.

ENHANCING an EXISTING PROGRAM

Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship
A joint SHEA/IDSA task force presents guidelines for developing institutional programs to enhance antimicrobial stewardship, an activity that includes appropriate selection, dosing, route and duration of antimicrobial therapy. These guidelines, published in the journal Clinical Infectious Diseases, focus on the development of effective hospital-based stewardship programs and do not include specific outpatient recommendations. To download, go to http://bit.ly/1lOKSCO.

Policy Statement on Antimicrobial Stewardship by SHEA, IDSA and PIDS
This position statement recommends the mandatory implementation of antimicrobial stewardship throughout the health care continuum, suggests process and outcome measures to monitor these interventions and addresses deficiencies in education and research in this field as well as the lack of accurate data on antimicrobial use in the United States. To download, go to http://bit.ly/1q5Iakw.

ASHP Statement on the Pharmacist’s Role in Antimicrobial Stewardship and Infection Prevention and Control
Pharmacists have a responsibility to take prominent roles in ASPs and participate in the infection prevention and control programs of hospitals and health systems. Pharmacists’ responsibilities for antimicrobial stewardship and infection prevention and control include promoting the optimal use of antimicrobial agents, reducing the transmission of infections and educating health professionals, patients and the public. To download, go to http://bit.ly/1qHxaDu.

CDC Vital Signs: Improving Antibiotic Use among Hospitalized Patients
Antibiotic prescribing for inpatients is common, and there is ample opportunity to improve use and patient safety by reducing incorrect antibiotic prescribing. Hospital administrators and health care providers can reduce potential harm and risk for antibiotic resistance by implementing formal programs to improve antibiotic prescribing in hospitals. To download, go to http://bit.ly/1q5ImJA.

Guidelines for the Prevention of Antimicrobial Resistance in Hospitals
This joint SHEA/IDSA task force publication details how antimicrobial resistance results in increased morbidity, mortality and costs of health care. Prevention of the emergence of resistance and the dissemination of resistant microorganisms will reduce these adverse effects and their attendant costs. Appropriate antimicrobial stewardship that includes optimal selection, dose and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among micro-organisms. A comprehensively applied infection control program will interdict the dissemination of resistant strains. To download, go to http://bit.ly/1InJDZT.

On the CUSP: Stop CAUTI Supplement from APIC
This supplement features success stories from facilities that have joined the On the CUSP: Stop CAUTI program, strategies for engaging others in CAUTI prevention, insight from experts on the program’s core national faculty, ways for health care organizations to be part of the program and frequently asked questions. To download, go to http://bit.ly/1o0v7qX.
**Clinician Resources**

**IMPLEMENTATION GUIDES and TOOLS**

**Assessment of Appropriateness of Antibiotics**

The primary goal of antibiotic stewardship efforts is to optimize the use of antibiotics. However, assessing “optimal” or “appropriate” antibiotic use remains a challenge. To begin addressing the challenge, CDC, in consultation with a variety of external experts, has developed assessment tools that can help facilities explore potential opportunities for improving antibiotic use. These forms draw heavily from existing treatment guidelines to identify variations in diagnostic evaluation and antibiotic use that deviate from general recommendations, such as:

- Urinary Tract Infections
- Community-Acquired Pneumonia
- Resistant Gram-Positive Infections
- Inpatient Antibiotics

**Tools and Sample Forms**

This resource, from SHEA’s Antimicrobial Stewardship task force, includes tools such as an adult inpatient antibiotic approval form, a blank order set for antifungal therapy, a sample checklist, a drug use evaluation form and others. To view the materials and forms, go to [http://bit.ly/1kPhoTG](http://bit.ly/1kPhoTG).

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**RESOURCES and ARTICLES**

**“Antimicrobial Stewardship: A Collaborative Partnership between Infection Preventionists and Health Care Epidemiologists” from APIC**

Infection preventionists and health care epidemiologists play key roles in promoting effective antimicrobial stewardship in collaboration with other health professionals, according to a joint position paper published by APIC and SHEA in their respective peer-review journals, the *American Journal of Infection Control* and *Infection Control and Hospital Epidemiology*. To download, go to [http://bit.ly/1l7ZPyo](http://bit.ly/1l7ZPyo).

**Infection Prevention + Antimicrobial Stewardship = Synergy**

In the APIC quarterly member magazine, *Prevention Strategist*, Julia Moody, MS, SM (ASCP), shares a case study and explains the infection preventionist’s and health care epidemiologist’s role in antimicrobial stewardship. To download, go to [http://bit.ly/1INwAR4](http://bit.ly/1INwAR4).
Clinical and Economic Outcomes of a Prospective Antimicrobial Stewardship Program

In ASHP’s American Journal of Health-System Pharmacy, the authors found antimicrobial expenditures, which had increased by an average of 14.4 percent annually in the years preceding ASP implementation, decreased by 9.75 percent in the first year of the program and remained relatively stable in subsequent years, with overall cumulative cost savings estimated at $1.7 million. Rates of nosocomial infections involving Clostridium difficile, methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci all decreased after ASP implementation. To download, go to http://bit.ly/Vl7JuV.

Antimicrobials and Resistance

This chapter from the 4th edition of APIC Text of Infection Control and Epidemiology discusses that although infection prevention traditionally has approached the problem of resistance primarily from the aspect of preventing transmission, more needs to be done to control how antimicrobials are commonly used. To download, go to http://bit.ly/VlfL75 and click on the blue bar that reads, “Download a free chapter of the APIC Text on ‘Antimicrobials and Resistance.’”

ASHP Guidelines on Pharmacist-Conducted Patient Education and Counseling

A coordinated effort among health care team members will enhance patients’ adherence to pharmacotherapeutic regimens, monitoring of drug effects and feedback to the health system. ASHP believes these patient education and counseling guidelines are applicable in all practice settings—including acute inpatient care, ambulatory care, home care and long-term care—whether these settings are associated with integrated health systems, managed care organizations or are freestanding. To download, go to http://bit.ly/1Nwau2.

Antimicrobial Stewardship and Clostridium difficile Infection: A Primer for the Infection Preventionist

This chapter, in Guide to Preventing Clostridium difficile Infections (CDI), an APIC Implementation Guide, discusses antimicrobial use and its impact on patients in all healthcare settings and ASPs within the context of CDI. To download, go to http://bit.ly/1iuCg3F.

APIC 2013 Clostridium difficile infection “Pace of Progress“ survey

Activities to stop the spread of the intestinal superbug Clostridium difficile (C. diff) are on the rise, but they are not yielding large improvements, according to a nationwide survey. According to the survey, 70 percent of infection preventionists have adopted additional interventions in their health care facilities to address CDI since March 2010, but only 42 percent have seen a decline in facility-associated CDI rates; 43 percent have not seen a decline. While CDI rates have climbed to all-time highs in recent years, few facilities (21 percent of respondents) have added more infection prevention staff to address the problem. To download, go to http://bit.ly/1q5JZr7.

Pediatric Stewardship Resources

Resources are available from SHEA that are specific to pediatric antimicrobial stewardship. To view, go to http://bit.ly/1knAzPv.

Research Bibliography

A bibliography on antimicrobial stewardship published in the Infection Control and Hospital Epidemiology journal available from SHEA can be found at http://bit.ly/1lo37gm.
WEBINARS

**Antimicrobial Stewardship: The Hospital Opportunity**
The webinar features Dr. Arjun Srinivasan of the CDC and Dr. Howard Gold of Beth Israel Deaconess Medical Center sharing compelling evidence for antimicrobial stewardship to improve care and lower cost. To register, go to http://bit.ly/1q5KjX0.

**Antimicrobial Stewardship: What the Infection Preventionist Needs To Know**
Provided by APIC, this webinar features Keith S. Kaye, MD, MPH who defines antimicrobial stewardship, discusses goals and components of an ASP, as well as details the role and collaboration of the infection preventionist with an antimicrobial stewardship team. To view, go to http://bit.ly/1rHoLO4.

**From Tragedy to Triumph to Trepidation: Antibiotics at Age 70**
Provided by APIC, this webinar features Stephen M. Brecher, PhD who explains how the war in England, then in the US, a famous fire in Boston and a football game all played a role in making penicillin the "Miracle Drug." With many new antibiotics, the war against infectious diseases seemed won. The problem, however, was that the bacteria did not read the press clippings. Antibiotics at Age 70 is the story of tragedy then triumph and now trepidation. To view, go to http://bit.ly/1mm08kS.

Patient Resources

**Antibiotics Aren’t Always the Answer**
This fact sheet from the CDC briefly explains six simple and smart facts about antibiotic use and when antibiotics can help treat your child’s illness. To download, go to http://bit.ly/1mc1Yo8.

**Cold or Flu. Antibiotics Don’t Work For You.**
This tri-fold brochure from the CDC briefly explains the difference between bacteria and viruses and how bacteria become resistant. It also answers some common questions about when it is and is not appropriate to use an antibiotic. To download, go to http://bit.ly/1pyTxHt.

**Ask Questions about Your Medicines**
This guide from APIC explains to patients when antibiotics work, when they don’t and when prescribed why it's important to finish the course of antibiotics as the prescriber recommends. To view, go to http://bit.ly/1o0wmGw.

**FAQs about Clostridium difficile**
A list of common patient questions about CDI, such as who is most likely to get it, how it is treated and how contraction can be prevented are included in this handout co-sponsored by SHEA, IDSA, AHA, APIC, CDC and The Joint Commission. To download, go to http://bit.ly/1rvhzo6.

**What You Need to Know about Clostridium difficile**
This article from APIC explains what *Clostridium difficile* is, the symptoms, who is at risk, how it’s diagnosed, treated and can be prevented. To view, go to http://bit.ly/1mc2jY6.
Strategies to Prevent Central Line–Associated Bloodstream Infections in Acute Care Hospitals: 2014 Update

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Received March 12, 2014; accepted March 13, 2014; electronically published June 9, 2014.

Infect Control Hosp Epidemiol 2014;35(7):753-771
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PURPOSE
Previously published guidelines are available that provide comprehensive recommendations for detecting and preventing healthcare-associated infections (HAIs). The intent of this document is to highlight practical recommendations in a concise format designed to assist acute care hospitals in implementing and prioritizing their central line–associated bloodstream infection (CLABSI) prevention efforts. This document updates “Strategies to Prevent Central Line–Associated Bloodstream Infections in Acute Care Hospitals,” published in 2008. This expert guidance document is sponsored by the Society for Healthcare Epidemiology of America (SHEA) and is the product of a collaborative effort led by SHEA, the Infectious Diseases Society of America (IDSA), the American Hospital Association (AHA), the Association for Professionals in Infection Control and Epidemiology (APIC), and The Joint Commission, with major contributions from representatives of a number of organizations and societies with content expertise. The list of endorsing and supporting organizations is presented in the introduction to the 2014 updates.

SECTION 1: RATIONALE AND STATEMENTS OF CONCERN

I. Patients at risk for CLABSIs in acute care facilities
A. Intensive care unit (ICU) population: the risk of CLABSI in ICU patients is high. Reasons for this include the frequent insertion of multiple catheters, the use of specific types of catheters that are almost exclusively inserted in ICU patients and associated with substantial risk (eg, pulmonary artery catheters with catheter introducers), and the fact that catheters are frequently placed in emergency circumstances, repeatedly accessed each day, and often needed for extended periods of time.
B. Non-ICU population: although the primary focus of attention over the last 2 decades has been the ICU setting, the majority of CLABSIs occur in hospital units outside the ICU or in outpatients.
C. Infection prevention and control efforts should include other vulnerable populations, such as patients receiving hemodialysis through catheters, intraoperative patients, and oncology patients.
D. Besides central venous catheters (CVCs), peripheral arterial catheters also carry a risk of infection.

II. Outcomes associated with hospital-acquired CLABSI
A. Increased length of hospital stay.
B. Increased cost (the non-inflation-adjusted attributable cost of CLABSIs has been found to vary from $3,700 to $39,000 per episode).

III. Independent risk factors for CLABSI (in at least 2 published studies)
A. Factors associated with increased risk.
   1. Prolonged hospitalization before catheterization
   2. Prolonged duration of catheterization
   3. Heavy microbial colonization at the insertion site
   4. Heavy microbial colonization of the catheter hub
   5. Internal jugular catheterization
   6. Femoral catheterization in adults
I. Existing guidelines and recommendations to prevent CLABSI

A. Several governmental, public health, and professional organizations have published evidence-based guidelines and/or implementation aids regarding the prevention of CLABSI, including the following:

1. The Healthcare Infection Control Practices Advisory Committee (HICPAC), Centers for Disease Control and Prevention
2. The Institute for Healthcare Improvement
3. The Agency for Healthcare Research and Quality
4. The American Pediatric Surgical Association Outcomes and Clinical Trials Committee
5. The Joint Commission
6. APIC
7. The Infusion Nurses Society

B. The recommendations in this document focus on CVCs unless noted otherwise. These recommendations include recommendations based on evidence that supports the impact of the intervention in select settings where the quality of evidence is low, or where evidence is not stratified on the basis of catheter type (eg, tunneled, implanted, cuffed, noncuffed catheter, and dialysis catheter) and may not be applicable for prevention of bloodstream infections with other intravascular devices.

II. Infrastructure requirements include the following:

A. An adequately staffed infection prevention and control program responsible for identifying patients who meet the surveillance definition for CLABSI.
B. Information technology to collect and calculate catheter-days as a denominator when computing rates of CLABSI and patient-days to allow calculation of CVC utilization. Catheter-days from information systems should be validated against a manual method, with a margin of error no greater than ±5%.
C. Resources to provide appropriate education and training.
D. Adequate laboratory support for timely processing of specimens and reporting of results.

SECTION 2: BACKGROUND—STRATEGIES TO DETECT CLABSI

1. Surveillance protocol and definition of CLABSIs

   A. Use consistent surveillance methods and definitions to allow comparison to benchmark data.

   1. Recent data suggest that interrater reliability using NHSN definitions is lower than expected. This may also affect the reliability of public reporting. Additionally, the NHSN surveillance definition for CLABSI is different from the clinical definition for catheter-related bloodstream infection.

SECTION 3: BACKGROUND—STRATEGIES TO PREVENT CLABSI

1. Existing guidelines and recommendations

   A. Several governmental, public health, and professional organizations have published evidence-based guidelines and/or implementation aids regarding the prevention of CLABSI, including the following:

   1. The Healthcare Infection Control Practices Advisory Committee (HICPAC), Centers for Disease Control and Prevention
   2. The Institute for Healthcare Improvement
   3. The Agency for Healthcare Research and Quality
   4. The American Pediatric Surgical Association Outcomes and Clinical Trials Committee
   5. The Joint Commission
   6. APIC
   7. The Infusion Nurses Society

   B. The recommendations in this document focus on CVCs unless noted otherwise. These recommendations include recommendations where the potential to impact CLABSI risk clearly outweighs the potential for undesirable effects. Special approaches include recommendations where the intervention is likely to reduce CLABSI risk but where there is concern about the risks for undesirable outcomes, where the quality of evidence is low, or where evidence supports the impact of the intervention in select settings (eg, during outbreaks) or for select patient populations. Hospitals can prioritize their efforts by initially focusing on implementing the prevention approaches listed as basic practices. If CLABSI surveillance or other risk assessments suggest that there are ongoing opportunities for improvement, hospitals should then consider adopting some or all of the prevention approaches listed as special approaches. These can be implemented in specific locations or patient populations or can be implemented hospital-wide, depending on outcome data, risk assessment, and/or local requirements. Each infection prevention recommendation is given a quality-of-evidence grade (see Table 1).

   Note that some of the following measures have been combined into a “prevention bundle” that focuses on catheter insertion (eg, measures B.2, B.3, B.6, B.7, and C.3). Numerous studies have documented that use of such bundles is effective, sustainable, and cost-effective in both adults and children. Bundles are most likely to be successful if implemented in a previously established patient safety culture, and their success depends on adherence to individual mea-
TABLE 1. Grading of the Quality of Evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. High</td>
<td>Highly confident that the true effect lies close to that of the estimated size and direction of the effect. Evidence is rated as high quality when there is a wide range of studies with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval.</td>
</tr>
<tr>
<td>II. Moderate</td>
<td>The true effect is likely to be close to the estimated size and direction of the effect, but there is a possibility that it is substantially different. Evidence is rated as moderate quality when there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide.</td>
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<tr>
<td>III. Low</td>
<td>The true effect may be substantially different from the estimated size and direction of the effect. Evidence is rated as low quality when supporting studies have major flaws, there is important variation between studies, the confidence interval of the summary estimate is very wide, or there are no rigorous studies, only expert consensus.</td>
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Note. Based on Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)^257 and the Canadian Task Force on Preventive Health Care.258

However, recent data suggest that not all components of bundles may be necessary to achieve an effect on CLABSI rates.52 After catheter insertion, maintenance bundles have been proposed to ensure optimal catheter care.53 More data are needed to determine which components of the maintenance bundle are essential in reducing risk.54,55

I. Basic practices for preventing and monitoring CLABSI: recommended for all acute care hospitals

A. Before insertion

1. Provide easy access to an evidence-based list of indications for CVC use to minimize unnecessary CVC placement (quality of evidence: III).
2. Require education of healthcare personnel involved in insertion, care, and maintenance of CVCs about CLABSI prevention (quality of evidence: II).56-60
   a. Include the indications for catheter use, appropriate insertion and maintenance, the risk of CLABSI, and general infection prevention strategies.
   b. Ensure that all healthcare personnel involved in catheter insertion and maintenance complete an educational program regarding basic practices to prevent CLABSI before performing these duties.61,62 Periodic retraining with a competency assessment may be of benefit.63
   c. Ensure that any healthcare professional who inserts a CVC undergoes a credentialing process (as established by the individual healthcare institution) to ensure their competency before independently inserting a CVC.
   d. Reeducate when an institution changes components of the infusion system that requires a change in practice (eg, when an institution’s change of the needleless connector requires a change in nursing practice).
   e. Consider using simulation training for proper catheter insertion technique.64-66
3. Bathe ICU patients over 2 months of age with a chlorhexidine preparation on a daily basis (quality of evidence: I).67-70
   a. In long-term acute care hospitals, daily chlorhexidine bathing may also be considered as a preventive measure.71
   b. The role of chlorhexidine bathing in non-ICU patients remains to be determined.72
   c. The optimal choice of antiseptic agents is unresolved for children under 2 months of age. However, chlorhexidine is widely used in children under 2 months of age.73 A US survey found that in the majority of neonatal ICUs (NICUs) chlorhexidine products are used for catheter insertion in this age group.74 For chlorhexidine gluconate (CHG)–based topical antiseptic products, the Food and Drug Administration recommends “use with care in premature infants or infants under 2 months of age; these products may cause irritation or chemical burns.” The American Pediatric Surgical Association recommends CHG use but states that “care should be taken in using chlorhexidine in neonates and premature infants because of increased risk of skin irritation and risk of systemic absorption.”40 Concerns in children under 2 months have been noted elsewhere.75 Cutaneous reactions to CHG have also been reported in extremely-low-birthweight neonates under 48 hours of age;76 however, in a small pilot trial of neonates under 1,000 g and at least 7 days of age, severe contact dermatitis did not occur, although CHG was cutaneously absorbed.77 These findings have not been replicated in a recent trial in neonates weighing more than or equal to 1,500 g.78,79 Some institutions have used chlorhexidine-containing sponge dressings for CVCs80 and chlorhexidine for cleaning CVC insertion sites in children in this age group with minimal risk of such reactions.40 Providers must care-
fully weigh the potential benefit in preventing CLABSI in children under 2 months and the risks of CHG, recognizing that term and preterm infants may have different risks. Alternative agents, such as povidone-iodine or alcohol, can be used in this age group.45

B. At insertion

1. Have a process in place to ensure adherence to infection prevention practices at the time of CVC insertion in ICU and non-ICU settings, such as a checklist (quality of evidence: II).45,81,82
   a. Ensure and document adherence to aseptic technique.
      i. Checklists have been suggested to ensure optimal insertion practices. If used, the documentation should be done by someone other than the inserter.
      ii. Observation of CVC insertion by a nurse, physician, or other healthcare personnel who has received appropriate education (see above) to ensure that aseptic technique is maintained.
      iii. Such healthcare personnel should be empowered to stop the procedure if breaches in aseptic technique are observed.
   b. Use an alcohol-based waterless product or antiseptic soap and water.
   i. Use of gloves does not obviate hand hygiene.

2. Perform hand hygiene prior to catheter insertion or manipulation (quality of evidence: II).83-87
   a. Use an alcohol-based waterless product or antiseptic soap and water.
   i. Use of gloves does not obviate hand hygiene.

3. Avoid using the femoral vein for central venous access in obese adult patients when the catheter is placed under planned and controlled conditions (quality of evidence: I).26,27,113,114
   a. Additional factors may influence the risk of CLABSI in patients with femoral vein catheters.91,92
   b. Femoral vein catheterization can be done without general anesthesia in children and has not been associated with an increased risk of infection in this population.93
   c. Controversy exists regarding infectious and noninfectious complications associated with different short-term CVC access sites.89,94 The risk and benefit of different insertion sites must be considered on an individual basis with regard to infectious and noninfectious complications (eg, patients with jugular access may have a higher infection risk if they have a concurrent tracheostomy95).
   d. Do not use peripherally inserted CVCs (PICCs) as a strategy to reduce the risk of CLABSI.
      i. The risk of infection with PICCs in ICU patients approaches that of CVCs placed in the subclavian or internal jugular veins.96,97
      ii. The majority of CLABSI due to PICCs occur in non-ICU settings.98 The PICC-associated CLABSI risk may be different outside the ICU.

4. Use an all-inclusive catheter cart or kit (quality of evidence: II).
   a. A catheter cart or kit that contains all necessary components for aseptic catheter insertion has to be available and easily accessible in all units where CVCs are inserted.

5. Use ultrasound guidance for internal jugular catheterization (quality of evidence: II).99
   a. Ultrasound-guided internal jugular vein catheterization reduces the risk of CLABSI and of noninfectious complications of CVC placement.100

   a. Use maximal sterile barrier precautions.
      i. A mask, cap, sterile gown, and sterile gloves are to be worn by all healthcare personnel involved in the catheter insertion procedure.
      ii. The patient is to be covered with a large (“full-body”) sterile drape during catheter insertion.
   b. These measures must also be followed when exchanging a catheter over a guidewire.
   c. A prospective randomized study in surgical patients showed no additional benefit for maximal sterile barrier precautions;108 nevertheless, most available evidence suggests risk reduction with this intervention.

   a. Before catheter insertion, apply an alcoholic chlorhexidine solution containing more than 0.5% CHG to the insertion site.112
   i. The antiseptic solution must be allowed to dry before making the skin puncture.

C. After insertion

1. Ensure appropriate nurse-to-patient ratio and limit the use of float nurses in ICUs (quality of evidence: I).26,27,113,114
   a. Observational studies suggest that there should be a nurse-to-patient ratio of at least 1 to 2 in ICUs where nurses are managing patients with CVCs and that the number of float nurses working in the ICU environment should be minimized.

2. Disinfect catheter hubs, needleless connectors, and injection ports before accessing the catheter (quality of evidence: II).115-119
   a. Before accessing catheter hubs, needleless connectors, or injection ports, vigorously apply mechanical friction with an alcoholic chlorhexidine preparation, 70% alcohol, or povidone-iodine. Alcoholic chlorhexidine may have additional residual activity compared with alcohol for this purpose.120
   b. Apply mechanical friction for no less than 5 seconds to reduce contamination.121,122 It is unclear whether this duration of disinfection can be generalized to needleless connectors not tested in these studies.
4. For nontunneled CVCs in adults and children, change gauze dressings every 2 days or earlier if the dressing is soiled, loose, or damp (quality of evidence: II).129-131

5. Replace administration sets not used for blood, blood products, or lipids at intervals not longer than 96 hours (quality of evidence: II).132,133

6. Use antimicrobial ointments for hemodialysis catheter-insertion sites (quality of evidence: I).134-140

a. Polysporin “triple” (where available) or povidone-iodine ointment should be applied to hemodialysis catheter insertion if compatible with the catheter material.

i. Certain manufacturers have indicated that the glycol constituents of ointments should not be used on their polyurethane catheters.

b. Mupirocin ointment should not be applied to the catheter-insertion site due to the risks of facilitating mupirocin resistance and the potential damage to polyurethane catheters.


a. Measure the unit-specific incidence of CLABSI (CLABSI per 1,000 catheter-days) and report the data on a regular basis to the units, physician and nursing leadership, and hospital administrators overseeing the units.

b. Compare CLABSI incidence with historical data for individual units and with national rates (ie, NHSN).143

c. Audit surveillance as necessary to minimize variation in interobserver reliability.122,123

d. Surveillance for CLABSI outside the ICU setting requires additional resources.144 Electronic surveillance is an option in these settings.145

II. Special approaches for preventing CLABSI

A number of special approaches are currently available for use. Perform a CLABSI risk assessment before considering implementing any of these approaches, and take potential adverse events and cost into consideration. Although it is reasonable to evaluate the utility of technology-based interventions when CLABSI rates are above the institutional or unit-based threshold, this is also an opportunity to review practices and consider behavioral changes that may be instituted to reduce CLABSI risk. These special approaches are recommended for use in locations and/or populations within the hospital with unacceptably high CLABSI rates despite implementation of the basic CLABSI prevention strategies listed above. These measures may not be indicated if institutional goals have been consistently achieved.

1. Use antiseptic- or antimicrobial-impregnated CVCs in adult patients (quality of evidence: I).29,30,146-152

a. The risk of CLABSI is reduced with some currently marketed antiseptic-impregnated (eg, chlorhexidine–silver sulfadiazine) catheters and antimicrobial-impregnated (eg, minocycline–rifampin) catheters.

Use such catheters in the following instances.

i. Hospital units or patient populations have a CLABSI rate above institutional goals despite compliance with basic CLABSI prevention practices. Some evidence suggests that use of antimicrobial CVCs may have no additional benefit in patient care units that have already established a low incidence of catheter infections.153

ii. Patients have limited venous access and a history of recurrent CLABSI.

iii. Patients are at heightened risk of severe sequelae from a CLABSI (eg, patients with recently implanted intravascular devices, such as a prosthetic heart valve or aortic graft).

b. Monitor patients for untoward effects, such as anaphylaxis.154

2. Use chlorhexidine-containing dressings for CVCs in patients over 2 months of age (quality of evidence: I).80,155-160

a. It is unclear whether there is additional benefit to using a chlorhexidine-containing dressing if daily chlorhexidine bathing is already established and vice versa.

3. Use an antiseptic-containing hub/connector cap/port protector to cover connectors (quality of evidence: I).161-165

4. Use silver zeolite–impregnated umbilical catheters in preterm infants (in countries where it is approved for use in children; quality of evidence: II).166
a. Observational studies suggest that other antimicrobial-impregnated catheters appear to be safe and hold promise in pediatric ICU patients.167-169
5. Use antimicrobial locks for CVCs (quality of evidence: I).170-175
   a. Antibiotic locks are created by filling the lumen of the catheter with a supratherapeutic concentration of an antimicrobial solution and leaving the solution in place until the catheter hub is reaccessed. Such an approach can reduce the risk of CLABSI. Because of concerns regarding the potential for the emergence of resistance in exposed organisms, use antimicrobial locks as a preventative strategy for the following:
      i. Patients with long-term hemodialysis catheters.176
      ii. Patients with limited venous access and a history of recurrent CLABSI.
      iii. Patients who are at heightened risk of severe sequelae from a CLABSI (eg, patients with recently implanted intravascular devices, such as a prosthetic heart valve or aortic graft).
   b. To minimize systemic toxicity, aspirate rather than flush the antimicrobial lock solution after the dwell time has elapsed.177-180 For additional guidance, see the IDSA’s “Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection.”935
   6. Use recombinant tissue plasminogen activating factor once weekly after hemodialysis in patients undergoing hemodialysis through a CVC (quality of evidence: II).182
III. Approaches that should not be considered a routine part of CLABSI prevention
1. Do not use antimicrobial prophylaxis for short-term or tunneled catheter insertion or while catheters are in situ (quality of evidence: I).182-186
   a. Systemic antimicrobial prophylaxis is not recommended.
2. Do not routinely replace central venous or arterial catheters (quality of evidence: I).187-189
   a. Routine catheter replacement is not recommended.
IV. Unresolved issues
1. Routine use of needleless connectors as a CLABSI prevention strategy before an assessment of risks, benefits, and education regarding proper use.190-194
   a. Multiple devices are currently available, but the optimal design for preventing infections is unresolved. The original purpose of needleless connectors was to prevent needlestick injuries during intermittent use. No data regarding their use with continuous infusions are available.
2. Intravenous therapy teams for reducing CLABSI rates.77,195
   a. Studies have shown that an intravenous therapy team responsible for insertion and maintenance of peripheral intravenous catheters reduces the risk of bloodstream infections.196 However, few studies have been performed regarding the impact of intravenous therapy teams on CLABSI rates.
3. Surveillance of other types of catheters (eg, peripheral arterial or venous catheters).3,4
   a. Peripheral arterial catheters and peripheral venous catheters are not included in most surveillance systems, although they are associated with risk of bloodstream infection independent of CVCs.197,198 Future surveillance systems may need to include bloodstream infections associated with these types of catheters.
4. Estimating catheter-days for determining incidence density of CLABSI.
   a. Surveillance can be facilitated in settings with a limited workforce by estimating the number of catheter-days.199-201
5. Use of silver-coated catheter connectors are associated with reduced intraluminal contamination in ex vivo catheters.202
   a. There is a paucity of clinical evidence regarding the risk reduction with their routine use or use of other antimicrobial catheter connectors.
   a. A recent meta-analysis reported an association between CLABSI and transparent dressing use. However, the source studies for the meta-analysis reporting this association were of low quality.203
7. Impact of the use of chlorhexidine-based products on bacterial resistance to chlorhexidine.
   a. Widespread use of chlorhexidine-based products (eg, use of chlorhexidine bathing, antisepsis, and dressings) may promote reduced chlorhexidine susceptibility in bacterial strains.204 However, testing for chlorhexidine susceptibility is not standardized. The clinical impact of reduced chlorhexidine susceptibility in gram-negative bacteria is unknown.

SECTION 5: PERFORMANCE MEASURES
I. Internal reporting
   These performance measures are intended to support internal hospital quality improvement efforts205,206 and do not necessarily address external reporting needs. The process and outcome measures suggested here are derived from published guidelines, other relevant literature, and the opinion of the authors. Report process and outcome measures to senior hospital leadership, nursing leadership, and clinicians who care for patients at risk for CLABSI.
A. Process measures
   1. Compliance with CVC insertion guidelines as documented on an insertion checklist.
      a. Assess compliance with the checklist in all hospital settings where CVCs are inserted (eg, ICUs, emergency departments, operating rooms, radiology, and general nursing units) and assign a healthcare
personnel familiar with catheter care to this task. 

i. For an example of a central catheter checklist, see http://www.ihi.org/knowledge/Pages/Tools/CentralLineInsertionChecklist.aspx.

b. Measure the percentage of CVC insertion procedures in which compliance with appropriate hand hygiene, use of maximal sterile barrier precautions, and use of chlorhexidine-based cutaneous antiseptic of the insertion site is documented:

i. Numerator: number of CVC insertions that have documented the use of all 3 interventions (hand hygiene, maximal barrier precautions, and chlorhexidine-based cutaneous antiseptic use) performed at the time of CVC insertion.

ii. Denominator: number of all CVC insertions.

iii. Multiply by 100 so that the measure is expressed as a percentage.

2. Compliance with documentation of daily assessment regarding the need for continuing CVC access.

a. Measure the percentage of patients with a CVC where there is documentation of daily assessment:

i. Numerator: number of patients with a CVC who have documentation of daily assessment.

ii. Denominator: number of patients with a CVC.

iii. Multiply by 100 so that the measure is expressed as a percentage.

3. Compliance with cleaning of catheter hubs and injection ports before they are accessed (or compliance with use of antiseptic-containing port protectors).

a. Assess compliance through observations of practice:

i. Numerator: number of times that a catheter hub or port (or port protector) is observed to be cleaned before being accessed.

ii. Denominator: number of times a catheter hub or port (or port protector) is observed to be accessed.

iii. Multiply by 100 so that the measure is expressed as a percentage.

B. Outcome measures

1. CLABSI rate.

a. Use NHSN definitions.

i. Numerator: number of CLABSIs in each unit assessed (using NHSN definitions).

ii. Denominator: total number of catheter-days in each unit assessed (using NHSN definitions).

iii. Multiply by 1,000 so that the measure is expressed as the number of CLABSIs per 1,000 catheter-days.

iv. Risk adjustment: stratify CLABSI rates by type of patient care unit.207-209

(a) Report comparisons based on historical data and NHSN data, if available.143

II. External reporting

There are many challenges in providing useful information to consumers and other stakeholders while preventing unintended consequences of public reporting of HAIs.210,211 Recommendations for public reporting of HAIs have been provided by HICPAC,212 the Healthcare-Associated Infection Working Group of the Joint Public Policy Committee,213 and the National Quality Forum.214

A. State and federal requirements

1. Hospitals in states that have mandatory reporting requirements for CLABSI must collect and report the data required by the state.

2. For information on state and federal requirements, contact your state or local health department.

B. External quality initiatives

1. Hospitals that participate in external quality initiatives or state programs must collect and report the data required by the initiative or program.

2. Problems with interrater reliability may affect comparisons between different institutions.

SECTION 6: EXAMPLES OF IMPLEMENTATION STRATEGIES

Accountability is an essential principle for preventing HAIs. It provides the necessary translational link between science and implementation. Without clear accountability, scientifically based implementation strategies will be used in an inconsistent and fragmented way, decreasing their effectiveness in preventing HAIs. Accountability begins with the chief executive officer and other senior leaders who provide the imperative for HAI prevention, thereby making HAI prevention an organizational priority. Senior leadership is accountable for providing adequate resources needed for effective implementation of an HAI prevention program. These resources include necessary personnel (clinical and nonclinical), education, and equipment (Table 2).

Insertion of CVCs is one of the most common procedures performed at the patient’s bedside. The insertion procedure represents only one aspect of the risk for CLABSI, with the risk extending to all aspects of nursing care and maintenance during the CVC dwell time. CLABSI prevention strategies have expanded as new studies are published. Additionally, experience with implementing these strategies is increasing. This discussion will focus on strategies for engagement, education, execution, and evaluation of CLABSI prevention efforts. Published literature and expert opinion form the basis for the following recommendations.

I. Engage

The first step toward successful reduction of CLABSIs is to engage both frontline and senior leadership champions in the process and outcome improvement plan.215

A. Develop a multidisciplinary team that sets goals, defines the steps in the implementation process, and monitors
II. Educate

A. Change in human behavior is the goal of educational programs about CVC insertion, care, and maintenance.

B. Educational programs for all healthcare personnel involved with the insertion and care of all types of CVCs should address knowledge, critical thinking, behavior and psychomotor skills, and attitudes and beliefs. Identifying and analyzing gaps in these areas leads to the selection of measurable learning objectives, course content, and corresponding appropriate teaching strategies. The value of infection prevention should be emphasized throughout all education efforts.

C. Adult learners employ multiple ways to learn; therefore, multiple teaching strategies should be used. This includes self-directed study guides, instructor-led courses, and small- and large-group discussions. The planning group for the educational offering should have representatives from multiple professions, including physicians, nurse managers, staff nurses, infusion nurse specialists, and infection preventionists. The learner should be actively involved with the teaching methods, as lecture alone has been shown to be less effective with retention of information and changes in behavior. Delivery methods should be chosen on the basis of the learners’ needs and availability, along with the technical capabilities of the facility. This includes printed learning packages; audiovisual formats, such as slide presentations and videos; skills labs; journal clubs and nursing grand rounds; and computer-, Internet-, or DVD-based approaches.

Various educational methods and strategies have been studied to reduce CLABSI. In general, these educational interventions showed improvements in CLABSI rates; however, more study is needed to clearly understand the most effective teaching strategies, content taught, length of presentation, and frequency for repeating the program. Both extraluminal and intraluminal avenues for CVC infection should be addressed in the educational plan.

B. Focus on a culture of safety, which includes teamwork, technical processes, and promotion of accountability for prevention of CLABSI.

C. Make the problem real to all of those involved to increase buy-in. One strategy to accomplish this is to identify a patient in the unit who has suffered harm as a result of developing a CLABSI and then share that story with the team.

D. Identify and involve local champions. Engage infusion nurses or vascular access specialists as team members. Include formal (e.g., medical or nursing directors, charge nurses) and informal (e.g., frontline) leaders. Local champions increase the chance for success by engaging and educating peers, thereby increasing buy-in and ownership by all involved. These champions can influence the development of strategies that are a good match with the unit culture. Frequent communication between champions and frontline staff is imperative if concerns are to be resolved and improvement sustained.

E. Share the outcome data regularly with each unit. Data can be represented as the monthly CLABSI rate and/or the number of days since last infection. Consider reporting CLABSI rates as the standardized infection ratio (SIR). Displaying a trend line is also useful.

F. Utilize peer networks. Voluntary peer networking between hospitals can promote and ensure compliance with evidence-based practices. It also facilitates collaboration, performance evaluation, and accountability. All can benefit from best practices being shared, and brainstorming can be done to solve shared problems.

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packages of learning materials. Multiple delivery methods tailored to specific problems or issues and given intermittently over time produce greater reduction in CLABSI than a single structured offering or lecture.6,123

D. Other educational job aides should be readily accessible in the clinical setting for quick reminders and reinforcement of the appropriate procedures. This includes but is not limited to facility policies and procedures, posters, fact sheets, small pocket cards, e-mail messages, and messages via computer screen savers.25,27

E. To enhance patient safety, learning CVC insertion techniques requires a structured educational program focusing on knowledge acquisition and performance of insertions in a simulated environment, followed by supervised performance on patients. A meta-analysis of 20 studies using simulation for CVC insertion showed benefits in learner performance, knowledge, and confidence.66 Simulation for CVC insertion includes use of anatomical models and computer-based virtual reality.23 Other approaches have tried to simulate the “feel” of tissue puncture.239

F. All healthcare professionals should have documented competency with CVC insertion, care, and maintenance before being allowed to practice without direct supervision. A standardized competency assessment checklist should be used to assess and document competency of each individual performing CVC insertion and procedures related to care and maintenance (eg, dressing changes). Competency assessment checklists should be evaluated for interrater reliability and validity. The professional performing competency assessment of the learner should be competent with the procedure being assessed.220,240

G. Changes of products, devices, or technology used in the insertion and care of CVCs require adequate device training for all healthcare personnel expected to use the product(s). This training follows a period of device evaluation and its impact on CLABSI. Most device manufacturers employ personnel with clinical experience to provide product training, and this resource should not be overlooked.

H. Healthcare professionals using CVCs for infusion should have documented competency with all procedures, including but not limited to catheter stabilization, catheter dressing changes, intravenous administration set management, disinfection of needleless connectors, accessing implanted ports, and flushing and locking the CVC.43 This would involve demonstration of procedures in a simulation lab or in the clinical setting while being observed by a qualified professional.241,242

I. Assessment of educational programs includes the learner’s satisfaction with the program, changes in knowledge, and changes in work performance. Written tests are the most common form of measurement; however, this is limited to knowledge acquisition only and may produce anxiety in many adult learners. Other forms of assessment include contributions to group discussions and observation of performance using simulation. Measurement of healthcare professionals’ current level of knowledge about CVC insertion and care can provide valuable information for designing educational programs.243,244

J. Prior to an educational program, there should be planning for transfer of the learning from the classroom to the clinical setting. This includes patient care assignments to allow for application of new knowledge and practice of new skills, support and encouragement from leaders and managers, and the ability to follow up on issues or concerns that arise from clinical performance.

K. Education of the patient and/or family, as appropriate, is required for all CVC care procedures (eg, hand hygiene, dressing changes, intravenous administration set management, and flushing and locking), especially when transfer to an alternative setting (eg, home care, ambulatory setting) is planned.45,242

L. Education of facility administrators is necessary to ensure adequate funding and implementation of CLABSI prevention.242 Additionally, the goal of zero tolerance for CLABSI may be set by the chief officers of an institution; however, whether this goal can be reached depends on a number of factors.

III. Execute

A. Consider the use of quality improvement methodologies, such as Lean Six Sigma, Comprehensive Unit-Based Safety Program, Team STEPPS, Plan-Do-Study-Act, and the like, to structure prevention efforts. Various performance improvement tools can be used, such as dashboards and score cards, to share data with stakeholders.

B. Standardize care processes. This can be done through implementation of guidelines, bundles, and protocols that address both insertion and maintenance of central lines. Consider conducting structured daily multidisciplinary rounds. During rounds, discuss whether the patient still requires the central line, patient goals for the day, and potential barriers or safety issues.171 Empower staff to report process defects or barriers to implementation encountered to appropriate leadership. This can facilitate rapid intervention and process improvement. Assign accountability for adherence to specific departments or functions.

C. Create redundancy. Build redundancy or independent checks into the care delivery process to increase staff compliance. This can be done by incorporating visual cues as reminders for proper procedures. Implement a line insertion and line maintenance checklist both inside and outside ICUs. Consider the use of screen-saver messages, posters, banners, fact sheets, preprinted order
sets, pocket cards, and the like to educate and serve as reminders for staff.217,218

D. Consider participating in a CLABSI reduction collaborative. Collaboratives provide an organization with the opportunity to discover and share best practices and utilize comparative outcome data.

IV. Evaluate

A. Multidisciplinary teams should be used to form quality improvement collaboratives to set goals and identify the key factors to be measured. This team should have representatives from administration, all professions, and clinical nursing units.246,247 These teams may represent one hospital or many different hospitals.24,248,249

B. Evaluation involves both process and outcome measurement.246 Differences between age groups should also be considered (eg, neonates, pediatrics, and adults).24,249,250

C. Process measurement includes but is not limited to compliance with insertion bundles, CVC utilization by insertion site or type (eg, femoral catheters vs other CVC sites; PICCs vs centrally inserted lines), the condition of CVC dressing and timely dressing changes, and integrity and appropriate management of needless connectors, other add-on devices, and intravenous administration sets.43,251,252 Device utilization is defined as the number of catheter-days divided by the number of patient-days.245

D. Establish baseline compliance with evidence-based practices for line maintenance, such as the presence of clean and intact dressings.

E. Outcome measurement is the incidence rate of CLABSI and other infections associated with all types of vascular access devices (eg, exit-site infection, suppurative thrombophlebitis). Consider reporting CLABSI rates as SIR.

F. Process and outcome data should be linked to initial and ongoing competency assessment. Initial competency should be assessed at employment, after orientation, and with the introduction of new equipment or technology. Ongoing competency assessment is determined by process and outcome data with the facility deciding the frequency for repeated competency assessment.43

G. Measurement of education outcomes is needed on several levels. The learner’s satisfaction with the program is assessed by completion of the evaluation form immediately following completion of the program. This form also includes the learner’s self-assessment of achieving the learning objectives. The next level is measuring the change in learner’s knowledge, most often accomplished by comparison of scores on written pre- and posttests. The third level is to measure the actual change in behavior in clinical practice following the completion of the program. Using only the first and second levels of measurement will not ensure that a change in clinical behavior will occur.

Numerous factors affect CLABSI surveillance, including CVC type, CLABSI definition, blood culturing practices and written policies, laboratory practices, and staff attitudes and beliefs. Standardization of these factors facilitates benchmarking within and between organizations. Additionally, variations in these determinants could impact publicly reported CLABSI rates and influence reimbursement for hospital-acquired conditions.32,247

H. Surveillance for CLABSI outside the ICU is becoming more prevalent, especially with increasing use of electronic methods for data collection.253,254

I. Feedback to all healthcare staff is critical for the success of any evaluation program. Unit-based recognition of achievement of low CLABSI rates or the length of time between CLABSI events is a useful method to encourage staff involvement. The goals for improvement should be clearly and frequently articulated. Audit compliance with completion of insertion checklists and share this data with the staff. Other forms of feedback include periodic (eg, monthly, quarterly) communication (eg, e-mail messages, written reports) of process measurement data: posters, reports, or other forms of communication with graphs showing cumulative compliance with process measures.245,250,255,256

ACKNOWLEDGMENTS

Disclaimer. A.K.—The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Potential conflicts of interest. J.M. reports receiving a speaker honorarium from Gilead Sciences Switzerland. L.A.M. reports serving as an advisor/consultant for ICU Medical, Fresenius Medical Care, Bard Access Systems, Marvao Medical Devices, CareFusion, 3M Healthcare, Catheter Connections, Semprus Biosciences, and Sharklet Technologies. L.H. reports serving as an advisor/consultant for B Braun Medical, BD Medical, Excelsior Medical, Ivera Medical, Access Scientific, 3M, and Baxter Healthcare. A.M.P. reports receiving speaking fees from Bard and serving as a speaker and author for Covidien. M.E.R reports serving as an advisor/consultant for 3M, Ariste, Semprus, and Sharklet Technologies and receiving honoraria from Baxter and CareFusion. All other authors report no relevant conflicts of interest.

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An Optimized, Synthetic DNA Vaccine Encoding the Toxin A and Toxin B Receptor 1 Binding Domains of Clostridium difficile Induces Protective Antibody Responses In Vivo

Short title: Clostridium difficile DNA vaccine

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Abstract

*Clostridium difficile*–associated disease (CDAD) constitutes a large majority of nosocomial diarrhea cases in industrialized nations and is mediated by the effects of two secreted toxins, toxin A (TcdA) and toxin B (TcdB). Patients who develop strong antitoxin antibody responses can clear *C. difficile* infection and remain disease-free. Key toxin-neutralizing epitopes have been found within the carboxy terminal receptor-binding domain (RBD) of TcdA and TcdB, which has generated interest in developing the RBD as a viable vaccine target. While numerous platforms have been studied, very few data describe the potential of DNA vaccination against CDAD. Therefore, we created highly optimized plasmids encoding the RBD from TcdA and TcdB in which any putative N-linked glycosylation sites were altered. Mice and non-human primates were immunized intramuscularly followed by *in vivo* electroporation, and in these animal models, vaccination induced significant levels of both anti-RBD antibodies (blood and stool) as well as RBD-specific antibody-secreting cells. Further characterization revealed that sera from immunized mice and non-human primates could detect RBD protein from transfected cells as well as neutralize purified toxins in an *in vitro* cytotoxicity assay. Mice that were immunized with plasmids or given non-human primate sera were protected from a lethal challenge with purified TcdA and/or TcdB. Moreover, immunized mice were significantly protected when challenged with *C. difficile* spores from homologous (VPI 10463) and heterologous, epidemic (UK1) strains. These data demonstrate the robust immunogenicity and efficacy of a TcdA/B RBD-based DNA vaccine in preclinical models of acute toxin-associated and intragastric, spore–induced colonic disease.
**Author summary**

*Clostridium difficile* is a gram positive, anaerobic bacterium that is a significant cause of antibiotic-associated diarrhea worldwide. Within infected individuals, *C. difficile* produces two toxins (toxin A and toxin B) that interact with intestinal cells, resulting in cellular injury and death. Each toxin molecule possesses a receptor-binding domain (RBD) that mediates these cellular interactions. Importantly, the RBD contains several recognition sequences that allow antibodies to bind and neutralize toxin activity. In this study, we designed and characterized vaccine plasmids that express either the toxin A RBD or toxin B RBD. To accomplish this task, we applied several RNA/DNA-optimization strategies aimed at enhancing protein production and secretion. We show that immunization of both mice and non-human primates produced a multi-isotype humoral response consisting of robust levels of toxin-neutralizing antibodies. Furthermore, actively and passively immunized strategies in mice were employed to demonstrate protection against a lethal exposure to purified *C. difficile* toxins as well as an intragastric spore challenge. Our findings suggest that a DNA vaccine containing the RBD sequences from both toxin A and toxin B is immunogenic and would be a viable platform for preventing *C. difficile*-associated disease.
Introduction

*Clostridium difficile* infection is the leading cause of nosocomial antibiotic-associated diarrhea in developed countries, with 500,000 new infections and 20,000 deaths occurring annually in the United States alone (1). The primary cause of *C. difficile*-associated disease (CDAD) is antibiotic disruption of the gastrointestinal microflora followed by subsequent overgrowth of *C. difficile*. Morbidity and mortality associated with CDAD have risen over the past decade (2-4), due most likely to an increased prevalence of relapsing disease and emerging hypervirulent strains (2, 3). CDAD is mediated by the effects of two secreted toxins, toxin A (TcdA) and toxin B (TcdB), both of which disrupt the actin cytoskeleton in the gastrointestinal epithelium, leading to fluid accumulation and inflammation (5). Treating this disease is inherently difficult given the persistence of *C. difficile* spores within the hospital environment and the lack of standard and effective therapy for recurrent disease. Therefore, preventing morbidity and mortality associated with new infections and recurrent disease may require a prophylactic treatment that can effectively prevent toxin-mediated cytopathology.

Expression of either TcdA or TcdB alone can cause CDAD in hamsters (6, 7); however, the majority of clinical isolates of *C. difficile* express both TcdA and TcdB (8). Consequently, the outcome of CDAD in hamsters and humans correlates well with the development of host-antibody responses to both TcdA and TcdB (9-11). In the hamster model, moreover, immunotherapy with antibodies recognizing both toxins reduces CDAD more effectively than antibodies targeting the toxins individually (10, 12, 13). Therefore, a vaccine that targets both virulence factors would be most desirable.

TcdA and TcdB share a functionally similar C-terminal receptor-binding domain (RBD) that mediates the binding of toxins to carbohydrate receptors on the surface of epithelial target cells (14). Toxins lacking the RBD are not cytopathic *in vitro* (15) and antibodies
recognizing epitopes within the RBD are capable of neutralizing the toxin \textit{in vitro} and \textit{in vivo} 
\cite{12, 16, 17}. Several studies have identified the RBD as a suitable target for a vaccine or 
immunotherapy. Parenteral delivery of TcdA RBD protein, or a monoclonal antibody 
directed against this region, protected mice from a lethal dose of TcdA \cite{18}. Secondly, 
human RBD-specific monoclonal antibodies prevented \textit{C. difficile}-induced mortality in 
hamsters \cite{12} and reduced the number of recurrent infections in humans \cite{19}. Despite their 
efficacy, these approaches have drawbacks that may limit their usefulness in the clinic. For 
example, protein-based vaccines may suffer from shorter \textit{in vivo} half-lives while monoclonal 
antibodies are expensive and time-consuming to mass-produce. 

These drawbacks highlight the need to develop alternative vaccines strategies such as 
DNA-based immunization against \textit{C. difficile} toxins. Advantages supporting this platform as 
an alternative vaccine strategy include ease of manipulation, low production costs, stability, 
and lack of a cold chain requirement \cite{20, 21}. Moreover, DNA vaccines can induce robust 
humoral responses in addition to strong cellular responses with the use of appropriate 
adjuvants or delivery techniques. Taken together, these advantages make newer, synthetic 
DNA-based immunizations a desirable vaccine modality for \textit{C. difficile}. In support of this 
idea, optimized plasmids encoding the C-terminal RBD from TcdA \cite{22} or the N-terminal 
enzymatic domains of TcdA and TcdB \cite{23} have been reported to be immunogenic and 
protect mice from lethal toxin challenges. In the latter study, however, a plasmid encoding 
the RBD from TcdB failed to elicit an antigen-specific humoral response. Given that TcdB is 
essential for \textit{C. difficile} virulence \cite{7} in addition to the strong association between recurrent 
disease and low serum antibodies recognizing TcdB RBD \cite{11}, we believe it to be imperative 
to develop a vaccine that contains both TcdA RBD- and TcdB RBD-expressing plasmids. 

In the present study, synthetic inserts encoding the RBD of \textit{C. difficile} TcdA and TcdB 
were evaluated for their ability to elicit toxin-specific neutralizing antibodies. Our findings
show that the RBD vaccine induces a robust multi-isotype humoral response in mice and non-human primates (NHPs) that is able to neutralize toxin \textit{in vitro}. Mice that were immunized with our plasmids or NHP sera were protected from \textit{C. difficile} toxin and spore challenges. Overall, our work demonstrates that a synthetic DNA vaccine encoding the toxin RBDs is able to provide robust neutralizing and protective immune responses in small and large animal models.
Materials and Methods

Ethics Statement. In vivo electroporation of DNA vaccines in mice were conducted in accordance with the guidelines set forth by the National Institutes of Health and performed under protocols approved by the Institutional Animal Care and Use Committee at Drexel University College of Medicine (IACUC and Biosafety protocol 18489). Indian rhesus macaques (Macaca mulatta) were housed at the Tulane National Primate Research Center (Covington, LA) according to the standards and guidelines set forth in the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals in addition to the animal care standards deemed acceptable by the Association for the Assessment and Accreditation of Laboratory Animal Care International (TNPRC IACUC P0040R). All animal work was carried out in accordance with and approved by the Army Medical Research and Materiel Command (USAMRMC) Animal Care and Use Review Office (ACURO) as required by the Department of Defense.

Cell culture. HEK-293T/17 (American Type Culture Collection [ATCC] CRL-11268) and Vero 76 (ATCC CRL-1587) cells were cultured in complete growth medium (Dulbecco’s modified Eagle medium supplemented with 10% fetal bovine serum and 1% antibiotic-antimycotic). Cells were incubated in a 5% CO₂ humidified incubator at 37°C.

DNA vaccine construction and confirmation of antigenic protein expression. Plasmids expressing TcdA RBD or TcdB RBD were constructed as described previously [23]. Sequences for TcdA RBD (residues 1848–2710) and TcdB RBD (residues 1851–2366) from C. difficile strain VPI 10463 were obtained from GenBank (accession numbers CAJ67494 and CAJ67492, respectively). RBD sequences underwent RNA optimization in order to enhance protein expression and were constructed with a Homo sapiens codon bias (GeneArt,
Within the RBD sequence, putative N-linked glycosylation sites were disrupted by substituting a glutamine for the initial asparagine residue at each site. Therefore, two constructs were synthesized for each RBD antigen: unmodified (wild-type) and modified (N→Q). Constructs for TcdA RBD and TcdB RBD were independently inserted into the pVAX1 expression vector (GeneArt). The resulting constructs are referred to as pARBD-wt, pARBD-NQ, pBRBD-wt and pBRBD-NQ.

In vitro expression of plasmids was verified by transfecting HEK-293T cells (3.0 \times 10^5 cells) using Lipofectamine 2000 (Life Technologies). Forty-eight hours after transfection, cellular lysates and supernatants were harvested and fractionated using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (10%), and transferred to polyvinylidene fluoride membrane (Millipore, Billerica, MA). Immunodetection of vaccine antigens in vitro was performed with specific mouse antiserum and the expressed proteins were visualized using horseradish peroxidase–conjugated rabbit antimouse IgG (Santa Cruz Biotechnology, Santa Cruz, CA) using an enhanced chemiluminescence detection system (Pierce, Rockford, IL). For analysis of glycosylation status, aliquots of lysates and supernatants were digested with 500U of peptide N-glycosidase F (PNGase F, New England Biolabs, Ipswich, MA) for 1 hour at 37°C and deactivated at 65°C for 15 min. Samples were subjected to SDS-PAGE and immunodetection as described above.

Generation of recombinant TcdA RBD and TcdB RBD for use as coating antigens in ELISA assays. The RBD region of TcdA and TcdB was amplified from either pARBD-NQ or pBRBD-NQ using primers designed to facilitate subcloning into the ligation-independent cloning prokaryotic expression vector pETHSUL as described (24). TcdA and TcdB RBD protein were overproduced in E. coli and purified using the subtractive purification strategy outlined in Zentner et al. (25)
Mouse strains, plasmid immunization and in vivo electroporation in mice. Six- to 8-week-old female C57BL/6 mice (Jackson Laboratories, Bar Harbor, ME) were housed in a temperature-controlled, light-cycled, specific-pathogen free facility at Drexel University College of Medicine. Plasmids were formulated in 0.25% bupivacaine-HCL (Sigma, St. Louis, MO) in isotonic citrate buffer. Initial dosing experiments consisted of groups containing either (a) 25μg of the control plasmid (pVAX1); (b) 25μg of antigenic plasmid (pARBD-NQ or pBRBD-NQ); or (c) a mixture of 10μg of antigenic plasmid plus 15 μg of pVAX1 such that each group received a total of 25μg DNA. Later experiments involved 10μg of each plasmid, delivered either independently or in combination. The vaccine was administered to isofluorane-anesthetized mice (n = 5/group) (each immunization was 2 weeks apart for a total of 3 immunizations). All immunizations (volume = 20μl) were administered into the right tibialis anterior muscle using an insulin syringe needle (28g) immediately followed by in vivo electroporation (CELLECTRA 2000, Inovio Pharmaceuticals, Blue Bell, PA) which entails placing a triangular, three-pronged array directly into the tibialis anterior muscle followed by two pulses of 0.2 A each delivered for 52 ms/pulse and separated by 1 second.

Splenocyte isolation and ELISpot assays. At endpoints designated in the figure legends, animals were sedated using isofluorane. Following sacrifice, spleens from each mouse were harvested and crushed into a single-cell suspension using a Stomacher 80 (Seward Laboratory Systems, Inc., Bohemia, NY). The resultant suspension was filtered through a 40-μm cell strainer (BD Biosciences, Franklin Lakes, NJ), washed, and incubated for 5 min at room temperature in ammonium-chloride-potassium lysing buffer (Gibco, Life Technologies) to induce hemolysis. All cells were washed, resuspended in medium (RPMI1640 plus 10%
fetal bovine serum and 1% antibiotic-antimycotic) and counted (cell viability is determined using trypan blue stain) using a Countess automated cell counter (Life Technologies).

B-cell ELISpots were carried out as described previously (26-29) with some modifications as described below. Briefly, 96-well plates (Mabtech, Inc., Cincinnati, OH) were coated with 0.5 µg/ml of toxoid A or toxoid B (List Biological Laboratories, Inc., Campbell, CA) overnight at 4°C. The following day, plates were washed and blocked for at least 2 hours with 1% bovine serum albumin. For detection of antigen-specific spots, 5.0 × 10⁴ splenocytes from each group of mice were added to each well in triplicate and incubated for 5 hours at 37°C, 5% CO₂. The plates were then washed and incubated with antimouse IgG-biotin overnight at 4°C. The following day, plates were washed and incubated with streptavidin-alkaline phosphatase for 1 hour at room temperature. The plates were washed and developed using substrate 5-bromo-4-chloro-3-indolyl-phosphate/nitro blue tetrazolium (BCIP/NBT) until distinct spots emerged. Plates were then rinsed with distilled water, dried overnight at room temperature, and spots were enumerated using an automated ELISpot reader (Cellular Technology Limited, Shaker Heights, OH). Data are represented as the number of antigen-specific spots, or antibody-secreting cells (ASCs), per million splenocytes.

Processing of fecal pellets. Fecal pellets were collected from vaccinated mice. Stool was dissolved in the following buffer in a specific weight/volume ratio. One gram of thawed stool was dissolved with 4 ml of PBS pH 7.5 supplemented with 0.05% Tween 20, 0.1% BSA, 0.02% sodium azide, and a cocktail of protease inhibitors (cOmplete protease inhibitor tablets, Roche, Nutley, NJ). The suspension was incubated for 15 minutes with frequent vortexing, and sediment was pelleted by centrifugation at 1200 rpm for 5 minutes. The fecal supernatant was centrifuged again at 16,000Xg for 15 minutes. Cleared supernatants were either immediately used for ELISA or frozen at -80°C.
Analysis of antigen-specific IgG in the serum of immunized animals. An ELISA was used to determine levels of antigen-specific IgG in mouse serum as described previously (30, 31). Mouse blood samples were harvested by submandibular bleed, and subsequently, sera were analyzed individually within each experimental group. Ninety-six-well enzyme immunoassay/radioimmunoassay plates (Costar, Fisher Scientific, Waltham, MA) were coated for 2 hours at room temperature or overnight at 4°C with 0.5 µg/ml of coating antigen (toxoid A or toxoid B [List Biologicals] or recombinant TcdA RBD or TcdB RBD (produced as described above). Plates were washed and blocked against nonspecific binding with 3% bovine serum albumin for at least 2 hours at room temperature. Sera from immunized mice were diluted in blocking buffer, added to wells in duplicate, and incubated at room temperature for 2 hours or overnight at 4°C. Bound antibodies were detected with horseradish peroxidase–labeled goat antimouse IgG, IgG1, IgG2a, IgG2b, IgG3, IgA, and IgM (all from Santa Cruz Biotechnology) and developed with substrate 3,3′,5,5′-tetramethylbenzidine (TMB) H₂O₂ (Pierce). The color reaction was stopped with 2N H₂SO₄, and the absorbance at 450 nm was read using an EL312 Bio-Kinetics microplate reader (BioTek Instruments, Inc., Winooski, VT).

Non-human primate husbandry and specimen collection schedule. Rhesus macaques (M. mulatta) were housed at the Tulane National Primate Research Center in accordance with the standards of the American Association for Accreditation of Laboratory Animal Care. Animals were allowed to acclimate for at least 30 days in quarantine prior to any immunization. All protocols were approved by the Tulane National Primate Research Center Animal Care and Use Committee.
Plasmid immunization and in vivo electroporation delivery in non-human primates.

Groups of female rhesus macaques (*Macaca mulatta*) of Indian origin aged 4 to 8 years (*n* = 4 per group) were used in the study. For immunizations, animals were anesthetized with ketamine (0.1 ml/kg) or tiletamine/zolazepam (0.06–0.10 ml/kg) and immunized at weeks 0, 6, 12, and 18 with 1.0 mg per construct of pTcdA RBD and pTcdB RBD. DNA was formulated in sterile water for injection and delivered into the quadriceps muscle in a total volume of 0.75 ml per injection followed by *in vivo* electroporation using the constant current CELLECTRA device (Inovio Pharmaceuticals, Inc.; Blue Bell, PA).

Collection of peripheral blood from non-human primates. Animals were bled every 2 weeks starting at 2 weeks prior to the first immunization. Animals were anesthetized with ketamine (0.1 ml/kg) or tiletamine/zolazepam (0.06–0.10 ml/kg) and blood samples were collected from the femoral vein using the Sarstedt S-Monovette collection system (Sarstedt; Nümbrecht, Germany) and placed into serum gel tubes to allow whole blood to coagulate. Specimens were shipped on cool packs overnight to Drexel University College of Medicine. Upon receipt, serum gel tubes were spun at 2000 x g for 15 minutes to separate serum from coagulated blood plug. Serum obtained after centrifugation was aliquoted and frozen until testing in ELISA assays.

Detection of non-human primate serum anti-toxin IgG by ELISA. To determine sera antibody titers against TcdA and TcdB, 96-well high-binding polystyrene plates (Corning, Lowell, MA) were coated overnight at 4 C with 0.5 μg/ml of coating antigen (toxoid A or toxoid B [List Biologicals] or recombinant TcdA RBD or TcdB RBD (produced as described above). Plates were washed and blocked against nonspecific binding with 3% bovine serum albumin for at least 2 hours at room temperature. Then, sera from immunized rhesus.
macaques were diluted in blocking buffer, added to wells in duplicate, and incubated at room

... temperature for 2 hours or overnight at 4°C. Bound IgG antibodies were detected with goat

antimacaque IgG-HRP (Nordic) at a dilution of 1:10,000 and developed with substrate

3,3′,5,5′-tetramethylbenzidine (TMB) H₂O₂ (Pierce). The color reaction was stopped with 2N

H₂SO₄, and the absorbance at 450 nm was read using an EL312 Bio-Kinetics microplate

reader (BioTek Instruments, Inc., Winooski, VT).

In vitro toxin neutralization. Before each experiment, the dose of purified toxin (List

Biologicals) that induces 100% cell rounding was determined using Vero cells. Vero cells

(5.0 × 10⁴) were seeded into 96-well plates 24 hours before the onset of the assay. The next
day, serial dilutions of mouse serum were made in growth medium. To each dilution, toxin

was added such that the final concentration of toxin was twice that which was needed to yield

100% cell rounding. This mixture was placed at 37°C, 5% CO₂ for 1 hour before being

applied to the Vero cell monolayer. After 20 to 24 hours, cell rounding was visualized using

phase-contrast microscopy, and data were represented as the percentage of total cells

displaying cytopathic effects (CPE) averaged from five separate fields per well. All samples

were tested in duplicate.

Challenge studies in mice. For challenge studies involving purified C. difficile toxin, mice

were immunized with pARBD-NQ or pBRBD-NQ (10 or 25μg) as described above. Five

weeks after the final immunization, mice were challenged intraperitoneally with 200μL of

toxin diluted in 1X Hank’s buffered saline solution (HBSS). pARBD-NQ-immunized mice

received 300ng of TcdA, while pBRBD-NQ-immunized mice received 150ng each of TcdA

and TcdB. Alternatively, a 1:20 dilution of sera from immunized NHPs was diluted in sterile

HBSS and heat-inactivated at 55°C for 30 min. This was added to lethal amounts of TcdA +
TcdB (LD$_{100}$ determined prior to experiment) as described above and delivered intraperitoneally to naïve mice. All challenged mice were monitored daily for signs of morbidity (hunched posture, ruffled fur, abdominal hardening, hypothermia) and were sacrificed when at least three morbidities were observed.

For challenge studies involving *C. difficile* spores, mice were immunized with both pARBD-NQ and pRBD-NQ either twice or four times (Fig 7a). Control animals were either naïve or immunized with an equivalent amount of empty vector (pVAX1). After resting, animals were made susceptible to *C. difficile* infection by treatment with a broad-spectrum antibiotic cocktail (32) for seven days and subsequently challenged via oral gavage with $10^5$ CFU of spores of strains VPI 10463, a ribotype 087 strain, or UK1, a ribotype 027 strain, prepared as described (33). Infected animals were monitored daily for signs of sickness (e.g. diarrhea, hunched posture, lethargy and weight loss), and moribund animals were euthanized based on a rubric developed and approved by IACUC. Therefore, death is not an endpoint, as animals are euthanized if they display signs of disease/distress as determined by the rubric, although in rare cases, animals may succumb to infection prior to our twice daily checks for signs of rubric morbidity.

**Statistical analysis.** Statistical comparisons were performed using PASW SPSS v20 (IBM Corporation, Armonk, NY). All data were non-parametric; therefore, statistical differences were assessed between immunization groups using either a Mann-Whitney U or Kruskal-Wallis test. To assess differences within groups over time, we applied a Wilcoxon matched pairs test. A log-rank analysis was performed to determine significant differences between groups within the challenge studies. All data are presented as the median + range calculated from the averages of duplicate or triplicate wells for each animal. A $p$-value $\leq 0.05$ was
considered to be significantly different and denoted with an asterisk: * (≤0.05), ** (≤0.01), *** (≤0.001).
Results

Construction and expression of synthetic DNA vaccines expressing the RBD from TcdA and TcdB

The C-terminal RBDs of TcdA and TcdB are important for receptor-mediated endocytosis of the toxins (34, 35) and several studies have demonstrated the utility of the RBD as a vaccine candidate (12, 18, 19). In this study, we designed highly optimized plasmids based on the DNA sequence that defines the RBDs of TcdA and TcdB (36, 37) from the reference strain of *C. difficile* (VPI 10463). This was backtranslated *in silico* with the objective of introducing gene modifications that would enhance protein expression, including RNA and codon optimization (for *Homo sapiens*); introduction of both a Kozak element and an N-terminal IgE leader sequence; as well as removal of cis-acting motifs/RNA secondary structures that impede translation (21).

In order to avoid glycosylation of the expressed antigens, which could potentially mask key neutralization epitopes, we disrupted any putative N-linked glycosylation sites by introducing an Asn→Gln substitution at each site. This yielded a total of eight and three alterations within the TcdA RBD and TcdB RBD sequences, respectively (Fig 1a). These modified sequences were submitted for commercial synthesis and ligated into a pVAX1 vector, yielding plasmids that contain RBD inserts with either wild-type (RBD-wt) or altered (RBD-NQ) sequences (Fig 1b). The expression of RBD-NQ antigens was verified in transiently transfected 293T cells where RBD protein was detected in both cell lysates and supernatants (albeit at a lower level than for the wild-type protein) using antiserum raised against ARBD-wt or BRBD-wt (Fig 1c). To assess the glycosylation status of RBD-NQ protein *in vitro*, we transfected 293Ts with either pARBD-NQ, pBRBD-NQ, pARBD-wt, or pBRBD-wt and cell lysates were collected (Fig 1d). Digestion with PNGaseF, which cleaves posttranslational sugar modifications, resulted in a decreased molecular weight for RBD-wt.
but not for RBD-NQ protein. Taken together, these data demonstrate that pARBD-NQ and pBRBD-NQ express well in a mammalian cell line and that the Asn→Gln substitution does not interfere with recognition by polyclonal RBD-wt serum. Moreover, RBD-NQ protein is not sensitive to N-linked glycosylation in vitro.

Expression and immunogenicity of pARBD-NQ and pBRBD-NQ in mice

Immunogenicity of pARBD-NQ and pBRBD-NQ constructs was verified by analysis of sera from mice that were immunized three times intramuscularly followed by electroporation (IM/EP) (Fig 2a). Following the third IM/EP immunization, all mice displayed elevated levels of RBD-specific serum IgG (Fig 2b), demonstrating an increase over controls as high as 30- and 55-fold for pARBD-NQ and pBRBD-NQ, respectively (Fig 2c). As expected, animals immunized with empty vector (pVAX1) displayed negligible antigen-specific responses. Because lower titers of TcdA-specific IgM, IgG2 and IgG3 are characteristic of patients who have relapsing CDAD (38, 39), we investigated the isotype of the humoral immune response. Of note, a significant increase in absorbance for antigen-specific IgM, IgG1, IgG2a and IgG2b but not IgG3 nor IgA was observed in the serum of immunized mice as compared with controls (Fig 2d). To further confirm the immunogenicity of the constructs, we screened for RBD-specific ASCs in the spleens of immunized animals. After three IM/EP immunizations, there was a significant increase in the number of antigen-specific ASCs compared with control-immunized animals (Fig 2e). Considering that toxin-neutralizing antibodies (nAbs) are thought to be important for the control of CDAD (19), we tested the ability of vaccine-induced antibodies to neutralize toxin. Importantly, sera from immunized mice neutralized the cytopathic effects of TcdA and TcdB in a sensitive in vitro neutralization assay (Fig 3). Taken together, these data demonstrate that immunization with
either pARBD-NQ or pBRBD-NQ elicits antigen-specific and toxin-neutralizing humoral immune responses.

Protection of immunized mice following toxin challenge

Given that hyperimmune serum could neutralize C. difficile toxins in vitro, we next addressed whether immunization with pARBD-NQ and/or pBRBD-NQ could confer protective immunity in vivo. A lethal toxin challenge model was employed to directly assay for toxin-neutralizing antibodies within the serum. TcdA and/or TcdB were delivered intraperitoneally to naïve mice, and a lethal dose of TcdA was determined (LD<sub>100</sub> = 300 ng; unpublished data from our laboratory). No mortality was observed when the same dose of TcdB was administered alone, which is in accordance with previously published data (40). However, combining two sub-lethal doses of TcdA and TcdB (150 ng each) was lethal, and this regimen was used to challenge immunized mice.

Toxin-challenged mice were monitored daily for 7 days after the challenge, and the outcome was based on morbidity (e.g., lethargy and hunched posture) and mortality associated with this challenge model (32). Acute morbidities were observed in the majority of challenged animals within 72 hour of challenge. Compared with controls, all of which succumbed to challenge, 10/10 (100%) of animals immunized with 10 or 25 μg of pARBD-NQ were protected against TcdA challenge (Fig 4a). Interestingly, only those animals that received 25 μg of pBRBD-NQ were protected completely (10/10) from the dual toxin challenge (Fig 4b).

Immunogenicity of DNA vaccination in non-human primates

To determine whether pA/B RBD vaccination is immunogenic in a larger animal model, we performed NHP studies to detect post-vaccination humoral immune responses. Four
rhesus macaques were immunized IM/EP with both pARBD-NQ and pBRBD-NQ (Fig 5a).

Compared with their respective baseline timepoints, all four animals showed detectable levels of RBD-specific IgG in the serum as measured by ELISA (Fig 5b,c). Moreover, robust nAb responses towards both TcdA and TcdB were observed in the serum (Fig 6a). In contrast, all control animals remained negative throughout the course of the study.

We next tested the ability of the NHP immune sera to passively protect mice in an in vivo toxin neutralization assay. Sera collected 2 weeks after the fourth immunization was preincubated with a lethal dose of C. difficile toxin and delivered intraperitoneally to naïve mice. As seen in figure 6b, 56.5% (n=13/23) of mice survived challenge compared with controls. These data indicate that co-immunization with pARBD-NQ and pBRBD-NQ constructs is immunogenic in NHPs and that serum antibodies can neutralize toxin and protect mice from toxin-associated mortality.

Protection of immunized mice following spore challenge

Inducing CDAD in mice and hamsters requires pretreatment of animals with a cocktail of broad-spectrum antibiotics (32). This model mimics the fecal-oral route of transmission through intragastric delivery of purified C. difficile spores. Similar to what is observed during human infection, sickly mice will display symptoms of CDAD (e.g. watery stool and intestinal pathology) that may require euthanasia if these symptoms become too severe. To test our vaccine against a spore challenge using a clinically applicable vaccination schedule, we immunized animals twice and administered a lethal dose of spores from the homologous vaccine strain (VPI 10463). We found that after two immunizations with pARB-NQ and pRBD-NQ (10 μg each), we could detect robust RBD-specific IgG responses within the blood (Fig 7a) and stool (Fig 7b) that could neutralize toxin cytopathology in vitro (data not shown). After treating these mice with antibiotics, we observed 90% (n=9/10) protection.
from a homologous challenge compared with naïve controls (Fig 7d). All surviving animals experienced acute weight loss, peaking between days 3-5, followed by weight gain that stabilized by day 8 (Fig 7c). Finally, we were unable to prevent the onset of CDAD in antibiotic-treated mice by increasing the amount of DNA/immunization (data not shown). Because various toxin isoforms have been identified within clinical isolates and given the increasing prevalence of infections with hypervirulent strains, we thought to test our DNA vaccine against a clinically relevant, heterologous strain (UK1; B1/NAP1/027). As expected, pVAX-immunized mice, which were seronegative for RBD IgG (Fig 7e), responded poorly to challenge with UK1 spores. All animals developed signs of disease and 14.3% (n=1/7) of the animals were euthanized before the end of the experiment (Fig 7f,g). In contrast, after four immunizations with RBD-NQ plasmids, we observed RBD-specific serum antibody and 50% survival (n=4/8) after challenge. All animals in this experiment lost weight, but unlike the controls, weight loss in pRBD-immunized animals had either stabilized or begun to reverse by day 7 post-infection. Importantly, the protection observed in these experiments was seen at least 4 months after the final immunization, indicating that a strong, neutralizing memory response is maintained for at least several months using the DNA/electroporation platform.
Discussion

*Clostridium difficile*-associated disease has emerged as a primary health concern worldwide (41). Recently, an increased prevalence of infections has been observed among traditionally low-risk people, which is potentially attributable to the emergence of hypervirulent strains (42, 43). Considering that the majority of *C. difficile* clinical isolates express both TcdA and TcdB (44), the presence of both anti-TcdA and anti-TcdB antibodies would be optimal for providing robust protection from CDAD. Indeed, lower anti-toxin antibody responses are associated with elevated risk of infection and higher disease severity. Providing a strong humoral immune response has been the focus of several active and passive immunization approaches that are currently in clinical development. However, cost and stability issues will limit their effectiveness in domestic and foreign clinical settings. Alternative vaccination platforms, such as DNA vaccination, which are cost-effective and demonstrate a favorable safety profile in humans, should be the focus of current and future efforts to prevent CDAD.

In the current study, we designed plasmids expressing the C-terminal RBD regions of both toxins. In order to improve immunogenicity, the antigens were modified to disrupt putative N-linked glycosylation sites that could mask key neutralizing epitopes within the RBD. A key finding from our study is that these modified RBDs can serve as excellent immunogens, effective at producing a strong neutralizing antibody response that can prevent toxin-associated cytopathology *in vitro* as well as provide both active and passive protection of mice from challenges with lethal doses of TcdA and TcdB. Furthermore, our group is the first to report on a modified TcdB RBD-expressing plasmid that is immunogenic in both small and large animal models. We believe this discovery will not only enhance the success of these plasmids in future clinical trials but also improve the efficacy of any current or next-generation vaccines and therapies for CDAD.
Other groups have described plasmids expressing optimized TcdA RBD with an N-terminal tissue plasminogen activator (tPA) signal peptide sequence (22, 23). As expected, our plasmids, which encode N-linked glycan null RBDs, located downstream of a human IgE leader sequence, expressed well based on ELISA and Western blot analysis. RBD proteins generated from plasmids expressing wild-type inserts resolved at a higher molecular weight, which decreased upon treatment with PNGase F. Thus, wild-type RBD proteins possess bona fide N-linked glycosylation sites; however, due to the lower relative expression of RBD-NQ constructs, some of these sites may be needed to maintain a native structural conformation.

Immunization with either construct elicited a multi-isotype antigen-specific antibody response. A wider range of toxin-specific isotypes is advantageous for a C. difficile vaccine considering that a multi-isotype response may be more prevalent in asymptomatic carriers or nonrecurrent cases (1). Interestingly, we noticed a significant induction of antigen-specific IgG2a for both constructs. The presence of antigen-specific IgG2a suggests the involvement of a T cell component given that IFNγ is required to drive IgG2a class switching in activated murine B cells (45). Cellular immunity, however, is not known to be essential for control of CDAD, and future studies will be required to better understand the importance of T cells during infection. We do not believe that this response is due to an inherent quality associated with the RBD antigen. Instead, this is most likely a result of the potent adjuvanting properties of either EP, which can promote a broader range of isotypes to various antigens (46-49), or plasmid-incorporated cytosine phosphate guanosine nucleotide sequences, which signal through Toll-like receptor 9 and scavenger receptors.

In agreement with the ELISA data, we noticed that across all doses, sera from pARBD-NQ-immunized animals contained a more impressive level of toxin nAbs compared with pBRBD-NQ-immunized animals. Lower immunogenicity observed for pBRBD-NQ may be a result of lower secretion of BRBD-NQ protein (Fig 1c supernatant); however, this was not...
reflected in the serum of immunized mice. In order to assess the effectiveness of an RBD DNA vaccine, a challenge model is needed. To this end, delivery of purified *C. difficile* toxins intraperitoneally, either individually or in combination, is lethal in mice (50). However, systemic toxin is not indicative of a normal infection scenario since the majority of clinical manifestations of CDAD are self-limiting within the intestine (51). In life-threatening cases, however, systemic complications have been documented (52-56), and entry of the toxin into circulation is thought to be a possible cause (57). Therefore, challenging immunized mice with intraperitoneal toxin represents a stringent method for assaying the nAb response. Immunization with pARBD-NQ, at both doses, elicited sterilizing immunity to TcdA challenge, which is consistent with survival data of a previously described TcdA RBD DNA vaccine (22). In contrast, immunization with 25ug of pBRBD-NQ was required to elicit significant protection from challenge as compared to controls. This may be reflective of the higher nAb response observed for animals in this immunization group. Therefore, administration of a higher dose of pBRBD-NQ may be required to generate a titer of nAbs comparable to that of pARBD-NQ immunization.

In both mouse and hamster infection models of CDI, preventing infection-associated mortality is seen as an important metric of vaccine efficacy (12, 13, 22, 23, 58-66). Upon challenging pRBD-NQ-immunized animals with a lethal dose of spores, we observed 90% and 50% protection against homologous and heterologous strains, respectively. The partial protection seen with the heterologous UK1 challenge is likely due to a strain-dependent variation in toxin sequences. In fact, sequence alignments between VPI 10463 and hypervirulent strains (e.g. UK1) reveal that TcdA remains relatively well-conserved while the majority of heterology exists within the RBD of TcdB (67, 68). This creates a pattern of unique neutralizing epitopes such that polyclonal serum raised against TcdB RBD from VPI 10463 cannot cross-neutralize TcdB from UK1 *in vitro* (67). Although our challenge data do
not agree with this report, we believe that during an ongoing UK1 infection within our
immunized animals, either (1) TcdA is neutralized leaving insufficient TcdB to cause lethal
disease, or (2) TcdA and TcdB are both sufficiently neutralized indicating that in vitro toxin
neutralization assays do not accurately represent toxin-associated pathology within the
infected intestinal environment. Since the individual roles of TcdA and TcdB during a UK1
infection are unknown, future studies utilizing genetically-modified UK1 will aid in
answering this question.

Because we noticed a strong neutralizing antibody response and protection in mice, we
next wanted to assess whether the RBD DNA vaccines were immunogenic in NHPs. After
four immunizations, the NHP cohort displayed a robust level of RBD-specific serum IgG
similar to mice. Serum nAb responses for TcdA RBD were similar to what was observed in
mice. Importantly, in NHP serum as compared with mouse serum, TcdB RBD nAbs seemed
to prevent more CPE at similar dilutions (Fig 6). We further tested the nAb response of the
NHPs in an in vivo toxin neutralization assay. Hyperimmune NHP sera that are preincubated
with toxin protected a significant portion of mice (14/23) from challenge. While these
challenge studies were performed with immune sera taken after four immunizations, high
RBD-specific IgG levels were noted as early as two immunizations, which may be important
for clinical translation. Taken together, these data demonstrate that our RBD DNA vaccine is
immunogenic in a NHP model and can produce titers of nAbs that are protective in mice.

The ability of TcdA and TcdB to independently cause disease in animal models of
infection has highlighted the importance of targeting both toxins to prevent CDAD. Since this
discovery, several groups have attempted to incorporate both toxins in various vaccine
modalities. Recently, Jin et al attempted to create a TcdB RBD-expressing plasmid but it
failed to elicit immune responses after four immunizations with electroporation and
100µg/mouse (23). There are several differences between the design and delivery of pBRBD-
NQ that may account for differences in antigen expression: (1) inclusion of a larger segment of the TcdB C-terminus (526aa vs. 515aa); (2) use of different N-terminal signal peptide sequences (IgE vs tPA); and (3) use of different in vivo electroporation delivery systems. Since the crystal structure of TcdB RBD has not been resolved and there is a lack of comparative studies between the leader sequences and electroporation devices used in these studies, it is difficult to discern why BRBD-NQ is more immunogenic. However, we feel that the use of both a human IgE leader sequence and a potentially superior electroporation system, which have been proven clinically (69), will increase the success of these plasmids in future clinical trials. Specifically, utilizing the CELLECTRA® 2000 in vivo electroporation delivery method (Inovio Pharmaceuticals, Inc.), a DNA vaccine delivery platform that is currently being used in Phase I clinical trials for HIV (PENNVAX) and influenza prophylactic strategies and in Phase II clinical trials for HPV therapy (VGX-3100) is a strength of the work presented here. The results from this study establish the immunogenicity and protective efficacy of RBD-NQ and demonstrate that the immunogenicity of both ARBD-NQ and BRBD-NQ can be improved through co-delivery. In particular, levels of total antigen-specific and nAb responses to RBD-NQ were higher than in previously described RBD DNA vaccines (22, 23). This is especially important for preventing primary CDAD, which can manifest within 2-4 days after infection in animal models. For this reason, a shorter vaccination regimen, reliant upon boosting through either immunization or natural infection, would be ideal for preventing the onset of CDAD in high-risk patients. Such a vaccine strategy may be more attainable by utilizing a DNA prime-heterologous boost strategy, which has demonstrated superior immunogenicity profiles for several antigens in animal models and humans (70).


Figure 1. Construction and expression of a DNA vaccine encoding the RBDs from TcdA and TcdB.

(A) ARBD-NQ and BRBD-NQ inserts. Each insert contains a cytomegalovirus promoter with Kozak sequence, human IgE leader, and either the TcdA RBD or TcdB RBD followed by two stop codons. Within the RBD sequence, black lines indicate putative N-linked glycosylation sites that were altered. (B) These inserts were cloned into pVAX1 creating four plasmids: pARBD-wt, pARBD-NQ, pBRBD-wt, and pBRBD-NQ. (C) pARBD-NQ and pBRBD-NQ expression were confirmed in transfected HEK-293T cells. Forty-eight hours after transfection, immunodetection of RBD protein was performed on the lysates (30 µg) and supernatants (100 µg for A RBD and 150 µg for B RBD) using mouse RBD antiserum. (D) Similar amounts of lysates and supernatants were treated with PNGaseF and subjected to SDS-PAGE in order to assess the glycosylation of RBD proteins in vitro.

Figure 2. RBD DNA vaccination induces strong humoral responses in mice.

(A) C57BL/6 mice (n=5) were immunized three times (via intramuscular electroporation) with 10 or 25 µg of either pARBD-NQ (denoted as A) or pBRBD-NQ (denoted as B) Animals immunized with pVAX-1 are referred to as control. (B) After the third immunization, total serum anti-RBD IgG responses were measured by ELISA, and (C) compared at a 4500^1 dilution. (D) To determine the isotype of vaccine-induced RBD-specific antibodies, post–third immunization sera was subjected to a similar analysis. (E) Spleens from immunized animals were isolated 10 days after the third immunization. Pooled splenocytes were added to RBD- or IgG-coated ELISpot plates, and the number of antigen-specific ASCs were enumerated. Bars and lines indicate the median of each group.

Figure 3. Induction of toxin-neutralizing antibodies in mice.
Quantification of systemic (A) TcdA-specific or TcdB-specific nAbs from immunized mice.

Vero cells were exposed to mouse sera preincubated with either TcdA or TcdB, and the average cytopathic effect (CPE) across two wells was assessed under 10× magnification.

Media represents the effect of toxin in the absence of serum. Bars indicate the median for each group. (B) Representative images are included to display immune serum neutralizing the cytopathic effect of toxin.

**Figure 4. Survival of immunized mice challenged with TcdA and TcdB.**

(A) Immunization and challenge schedule for mice. C57BL/6 mice (n = 10/group) were immunized as described earlier and rested for 8 weeks before being challenged intraperitoneally with a lethal dose of *C. difficile* toxin. Animals immunized with pARBD-NQ (B) or pBRBD-NQ (C) were challenged with 300 ng of TcdA or 150 ng of both TcdA and TcdB, respectively.

**Figure 5. pRBD-NQ immunization elicits strong humoral responses in non-human primates.**

(A) Immunization schedule in NHPs. Female rhesus macaques (n = 4) were given 1.0 mg of both pARBD-NQ and pBRBD-NQ by intramuscular electroporation (IM/EP). NHPs received four immunizations spaced 6 weeks apart. (B) RBD-specific IgG was analyzed in post–fourth immunization sera (post 4th imm) and (C) were compared at a 5000⁻¹ dilution 2 weeks after each immunization. Bars and lines indicate the median for each group.

**Figure 6. Serum from immunized non-human primates neutralizes toxin in vitro and protects mice from a lethal intraperitoneal toxin challenge.**
(A) Quantification of systemic nAbs from immunized NHPs. The ability to neutralize TcdA and TcdB were assessed independently. Bars indicate the median for each group. (B) Sample images of neutralization are displayed. (C) NHP sera harvested after the final immunization was diluted (20^{-1}), heat-inactivated and combined with a lethal dose of TcdA + TcdB. This was delivered intraperitoneally to naïve animals and survival was measured over the course of five days. Control animals received baseline NHP sera.

Figure 7. RBD DNA immunization protects mice against experimental CDI.

Mice were immunized with 10 μg each of pRBD-NQ constructs and serum (A and E) as well as stool (B) anti-RBD IgG levels were measured. After two immunizations (C and D) or four immunizations (F and G), mice were challenged with *C. difficile* VPI 10463 or UK1 spores, respectively. Mouse weight loss and mortality are depicted (black line—pARBD-NQ + pBRBD-NQ; grey line—naïve (VPI 10463) or pVAX-immunized (UK1)). Experiments involving pRBD-NQ immunization were performed with 7-10 mice/group; *, P < 0.05.

Acknowledgements

We would like to acknowledge Dr. Linc Sonenshein for allowing MAK and SB to train in his laboratory on working in an anaerobic chamber to properly propagate and quantify *C. difficile* bacteria and spores for use in our studies. We would also like to thank Dr. Sonenshein for his expertise and guidance in working with *C. difficile* and providing the spore stocks for these studies. We acknowledge the Drexel University College of Medicine Office of Faculty Affairs and Professional Development for funding a Professional Enrichment and Growth grant so that MAK and SB could travel and spend an extended amount of time in Dr. Sonenshein’s lab to train. The PEG grant also partially funded the purchase of the anaerobic chamber. We would also like to acknowledge Drs. Rafi Ahmed,
Shane Crotty and Rachael Aubert for assay guidance for the murine B cell ELISpot assay.

This work was funded by a Congressionally Directed Medical Research Grant W81XWH-09-1-0382 (http://cdmrp.army.mil/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This work was supported in part with federal funds from the National Center for Research Resources and the Office of Research Infrastructure Programs (ORIP) of the National Institutes of Health through Grant Number P51 RR00164 to the Tulane National Primate Research Center. The authors wish to thank Dr. Jason Dufour and the Division of Veterinary Medicine for animal care and services at Tulane National Primate Research Center. We would like to acknowledge Diana Winters from Drexel University College of Medicine Academic Publishing Services for her editorial, formatting and journal submission expertise.

Conflict of Interest

Competing financial interests: D.B.W. has grant funding, participates in industry collaborations, has received speaking honoraria, and fees for consulting. This service includes serving on scientific review committees and advisory boards. Remuneration includes direct payments or stock/stock options and in the interest of disclosure therefore he notes potential conflicts associated with this work with in particular Inovio where he serves on the SAB as well as with Pfizer, Bristol Myers Squibb, Merck, Aldevron, Roche, Ferring Pharma and possibly others. Licensing of technology from his laboratory has created over 150 jobs in the private sector in the biotech/pharma industry. The other authors declare no competing financial interests.

To be used by health-care workers, trainers and observers of hand hygiene practices
SAVE LIVES
Clean Your Hands

Hand Hygiene

To be used by health-care workers, trainers and observers of hand hygiene practices
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DEFINITION OF TERMS

**Alcohol-based (hand) rub.**
An alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants.

**Clean/aseptic procedure**
Any care activity that implies a direct or indirect contact with a mucous membrane, non-intact skin or an invasive medial device. During such a procedure no germ should be transmitted.

**Body fluids**
Any substance/fluid from the body:
- blood
- excreted: urine, stools, vomit, meconium, lochia
- secreted: saliva, mucous, sperm, milk and colostrum, tears, wax, caseosa (until first bath)
- trans-/ex-sudate: pleural fluid, cerebrospinal fluid, ascites fluid, synovial fluid, amniotic fluid, pus, with the exception of sweat
- by extension, any biological samples taken from the body (including tissue sample, placenta, cytological sample, organ, bone marrow)

**Critical site**
Critical sites are associated with the risk of infection. They either correspond to body sites or to medical devices that have to be protected against germs (called critical sites with infectious risk for the patient), or body sites or medical devices that potentially lead to hand exposure to body fluids and blood borne pathogens (called critical sites with body fluid exposure risk). Both pre-cited risks can occur simultaneously.

**Medical gloves**
Gloves used for medical procedures:
- sterile and non-sterile examination gloves
- surgical gloves
- chemotherapy gloves

**Hand hygiene**
A general term referring to any action of hand cleansing. Hand-rubbing with an alcohol-based handrub or handwashing with soap and water aimed at reducing or inhibiting the growth of micro-organisms on hands.

**Hand hygiene indication**
Reason for a hand hygiene action.

**Hand hygiene opportunity**
Moment during health-care activities when hand hygiene is necessary to interrupt germ transmission by hands. It constitutes the denominator for calculating hand hygiene compliance, i.e. the proportion of times that HCWs perform hand hygiene of all observed moments when this was required.

**Handrubbing**
Applying an antiseptic handrub to reduce or inhibit the growth of microorganisms without the need for an exogenous source of water and requiring no rinsing or drying with towels or other devices.

**Invasive medical device**
A medical device inserted either through the skin or a mucous membrane or through a natural orifice.

**Colonization**
The presence and multiplication of microorganisms without tissue invasion or damage.

**Infection**
Invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms.
Health care-associated infection (HCAI) places a serious disease burden and has a significant economic impact on patients and health-care systems throughout the world. Yet good hand hygiene, the simple task of cleaning hands at the right time and in the right way, can save lives.

The World Health Organization (WHO) has developed evidence-based WHO Guidelines on Hand Hygiene in Health Care to support health-care facilities to improve hand hygiene and thus reduce HCAI.

The Hand Hygiene Technical Reference Manual has been developed to assist health-care workers to implement improvements in their facility as part of a multi-modal strategy and in accordance with the WHO Guidelines on Hand Hygiene in Health Care.

This Technical Reference Manual is designed for use in any health-care facility. It describes detailed hand hygiene information and is aimed at health-care workers, trainers and observers. It focuses on understanding, practising and teaching hand hygiene concepts, with the aim of helping others to understand its importance and application in the prevention of micro-organism cross-transmission. It is particularly important as it provides comprehensive information on the application of WHO’s “My 5 Moments for Hand Hygiene” approach and the practice of hand hygiene observation, as well as providing practical examples and visuals. Thus, it facilitates increased knowledge on both when and how health-care workers should perform, as well as observe, hand hygiene. It can be used to facilitate formal and informal training and education sessions and helps to support the process of evaluation and feedback in relation to hand hygiene observations. The ultimate goal is to support the reduction in acquisition of HCAI by improving hand hygiene practices and thus prevent the wasting of resources, and, save lives.
PART I
HEALTH CARE-ASSOCIATED INFECTION AND HAND HYGIENE

I.1 WHAT IS A HEALTH CARE-ASSOCIATED INFECTION AND WHAT IS ITS IMPACT ON PATIENT SAFETY?

Health care-associated infection (HCAI) – also referred to as nosocomial infection – is defined as “an infection occurring in a patient during the process of care in a hospital or other health-care facility that was not present or incubating at the time of admission. This also includes infections acquired in the hospital but appearing after discharge, and occupational infections among staff of the facility”. From the definition it is clearly understandable that the occurrence of this infection is linked to health-care delivery and that it may result, although not always, as a consequence of the failure of health-care systems and processes as well as of human behaviour. Therefore, it represents a significant patient safety problem.

HCAI occurs worldwide and affects hundreds of millions of patients both in developed and developing countries. In developed countries it complicates between 5-10% of admissions in acute care hospitals. In developing countries the risk is two-to-20 times higher and the proportion of infected patients can exceed 25%. Beyond causing physical and moral suffering to patients and their relatives, HCAIs represent a high cost to the health system and consume resources that could be spent on preventive measures or other priorities.

I.2 WHAT IS THE ROLE OF HANDS IN GERM TRANSMISSION?

Microorganisms (germs) responsible for HCAI can be viruses, fungi, parasites and, more frequently, bacteria. HCAI can be caused either by micro-organisms already present on the patient’s skin and mucosa (endogenous) or by micro-organisms transmitted from another patient or health-care worker or from the surrounding environment (exogenous). In most cases, health-care workers’ hands are the vehicle for transmission of microorganisms from the source to the patient but patients themselves may also be the source. Generally, microorganisms are transmitted from one patient to another, from one body site to another and from the environment to the patient or vice versa. Health-care workers’ hands can become progressively colonized by germs and potential pathogens during patient care. In the absence of hand hygiene, the longer the duration of care, the higher the degree of hand contamination and potential risks to patient safety.

The risk of transmission and potential harm applies at any time during health-care delivery, especially to immuno-compromised or vulnerable patients and/or in the presence of indwelling invasive devices (such as urinary catheter, intra-venous catheter, endotracheal tube, drains).

I.3 WHAT ROLE DOES HAND HYGIENE PLAY IN THE PREVENTION OF HCAI?

Several studies have clearly demonstrated that the implementation of well-structured infection control programmes is a cost-effective way to reduce HCAI. Some have shown that these results are also achievable in countries and health-care facilities with limited resources.

The foundations of infection control are built on a number of simple, well-established precautions proven to be effective and widely appreciated. "Standard Precautions" encompass the basic principles of infection control that are mandatory in all health-care facilities. Their application extends to every patient receiving care, regardless of their diagnosis, risk factors and presumed infectious status, reducing the risk to patient and staff of acquiring an infection.

Hand hygiene is very much at the core of Standard Precautions and is the undisputed single most effective infection control measure. This also includes circumstances where specific, targeted “isolation precautions” (namely contact, droplet and airborne precautions) are applied. Furthermore, its importance is emphasized in the most modern “bundle” or multimodal quality improvement approaches for the prevention of specific site infections such as device-related bloodstream and urinary tract infections, surgical site infection, and ventilator-associated pneumonia. The importance of embedding efficient and effective hand hygiene into all elements of care delivery must be kept prominent within health care.

I.4 HOW TO PRACTISE HAND HYGIENE?

Hand hygiene may be practised by rubbing hands with an alcohol-based handrub or by washing with soap and water. The technique for doing this, as well as the product used, render hands free from potentially harmful contamination and make them safe for patient care.
Handrubbing with an alcohol-based formulation

The most effective way to ensure optimal hand hygiene is by using an alcohol-based handrub. According to the WHO Guidelines on Hand Hygiene in Health Care, when an alcohol-based handrub is available, it should be used as the preferred means for routine hand antisepsis (recommendation IB). Alcohol-based handrubs have the following immediate advantages:

- elimination of the majority of germs (including viruses);
- the short time required (20 to 30 seconds);
- availability of the product at the point of care*;
- good skin tolerability;
- no need for any particular infrastructure (clean water supply network, washbasin, soap, hand towel).

Soap and alcohol-based handrub should not be used concomitantly (recommendation II).

To comply with routine hand hygiene recommendations, health-care workers should ideally perform hand hygiene where and when care is provided, which means at the point of care* and at the moments indicated. This often calls for the use of an alcohol-based product.

Hand washing

Hands need to be washed with soap and water when they are visibly dirty or soiled with blood or other body fluids, when exposure to potential spore-forming organisms is strongly suspected or proven, or after using the lavatory (recommendation II).

The process of performing effective hand hygiene, whether rubbing with an alcohol-based handrub or hand washing (Figures 1.a and 1.b), is dependent on a number of factors:

- the quality of the alcohol-based product (conformity with European and US standards)
- the amount of product used
- the time spent rubbing or washing
- the hand surface rubbed or washed.

Hand hygiene actions are more effective when hand skin is free of cuts, nails are natural, short and unvarnished, and hands and forearms are free of jewellery and left uncovered (see Section 4, Other aspects of hand hygiene).

It is therefore important that a number of steps are taken in the process of performing hand hygiene to render hands safe for providing care (Figures 1.a and 1.b).

I.5 WHEN TO PERFORM HAND HYGIENE?

Compliance or non-compliance with hand hygiene has consequences for the transmission of pathogens and the development of HCAIs. Hand hygiene is not just an option, a matter of common sense or merely an opportunity; it corresponds to indications during care delivery that are justified by the risk of germ transmission. To minimize differences in the way they are understood and applied by health-care workers, trainers and observers of hand hygiene practices it is important that hand hygiene indications become universally understandable. There should be no room for doubt or interpretation by health-care workers and, additionally, if hand hygiene practices are to be evaluated and fed back to ensure sustained improvement, it is essential that observers have a clear understanding of the right indications for hand hygiene.

*Point of care - the place where three elements come together: the patient, the health-care worker and care or treatment involving contact with the patient or his/her surroundings (within the patient zone). The concept embraces the need to perform hand hygiene at recommend-ed moments exactly where care delivery takes place. This requires that a hand hygiene product (e.g. alcohol-based handrub, if available) be easily accessible and as close as possible – within arm’s reach of where patient care or treatment is taking place. Point-of-care products should be accessible without having to leave the patient zone.

Availability of alcohol-based handrubs at point of care is usually achieved through staff-carried handrubs (pocket bottles), handrubs fixed to the patient’s bed or bedside table or handrubs affixed to dressing or medicine trolleys that are taken to the point of care.
I.5.1 The concept of “My five moments for hand hygiene”

The “My five moments for hand hygiene” concept proposes a unified vision for health-care workers, trainers and observers to minimize inter-individual variation and lead to a global increase in adherence to effective hand hygiene practices. Considering the evidence, this concept merges the hand hygiene indications recommended by the WHO Guidelines on Hand Hygiene in Health Care (see Part II of the Guidelines) into five moments when hand hygiene is required. Importantly, this user- and patient-centred approach aims for minimal complexity and a harmonious integration into the natural workflow, which applies across a wide range of care settings and health-care professions.

The decision to address hand hygiene via a synthetic concept focusing on only five indications is intended to make it easier to understand the moments when there is a risk of germ transmission via the hands, to memorize them and to assimilate them into health-care activities. The “My five moments for hand hygiene” (Figure 2) is proposed as the reference approach for the appropriate performance, teaching and evaluation of hand hygiene. The concept attempts to go beyond the long list (never exhaustive) of health-care actions and situations requiring hand hygiene; it does not define specific and multiple procedures and care situations but it helps focus on essential moments embedded within the care sequence that are essential for hand hygiene. The concept does not in any way reduce the need for hand hygiene. It is a tool to identify moments when hand hygiene must be performed, as well as to distinguish those when it is not useful.
II.1 APPLYING THE “MY FIVE MOMENTS FOR HAND HYGIENE” IN PRACTICE

The need for hand hygiene is closely connected with the activities of health-care workers within the geographical area surrounding each patient. Focusing on a single patient, the health-care environment can be divided into two virtual geographical areas, the patient zone and the health-care area, as illustrated in Figure 3.

II.1.1 The patient zone

The “My five moments for hand hygiene” are particularly focused on the contacts occurring within the patient zone during health-care delivery in this area. The patient zone includes the patient and some surfaces and items that are temporarily and exclusively dedicated to him or her. It contains the patient X and his/her immediate surroundings (Figure 3). This typically includes the patient and all inanimate surfaces that are touched by or in direct physical contact with the patient such as the bed rails, bedside table, bed linen, infusion tubing and other medical equipment. It further contains surfaces frequently touched by health-care workers while caring for the patient, such as monitors, knobs and buttons, and other touch surfaces.

Patient surroundings are contaminated by the patient’s own flora. Therefore, any item designed for reuse, should be previously decontaminated when entering and leaving the patient surroundings. Any item not usually dedicated to patient care and frequently moved to the health-care area should never be considered as patient surroundings, regardless of their proximity to the patient (e.g. the computerized or paper chart, pencils, etc). Personal belongings are considered part of patient zone since they should not be taken out of it. In addition items and surfaces temporarily exposed to the patient, such as surfaces of a shared bathroom, a table of physiotherapy or radiology should be decontaminated after the patient has left.

II.1.2 The health-care area

The health-care area corresponds to all surfaces in the health-care setting outside the patient zone of patient X, i.e. other patients and their patient zones and the wider health-care environment. In most settings the health-care area is characterized by the presence of various and
numerous microorganisms, including multi-resistant germs. Performing hand hygiene by applying the five moments for hand hygiene while caring for patients in their patient zone helps to protect the wider health-care environment from contamination by patients’ germs.

II.1.3 Contact with a patient and with his/her surroundings

The patient is a person receiving health care involving direct and indirect (via an intermediate object) contact.

The different types of contact are:

a) contact with patient’s intact skin and personal effects;
b) contact with mucous membranes, non-intact skin, an invasive medical device that corresponds to a critical site as far as the risk for the patient is concerned (e.g. a vascular access as shown in Figure 3);
c) potential or actual contact with a body fluid that corresponds to a critical site as far as the risk for the health-care worker is concerned (e.g. a urine bag as shown in Figure 3), including contact with mucous membrane and non-intact skin (critical sites at risk for exposure to body fluids); and
d) contact with objects in the patient surroundings.

Each type of contact justifies the need for one or more hand hygiene indications, preceding and following a procedure in order to prevent transmission either to the patient, to the health-care worker or to the health-care area.

II.2 THE HEALTH-CARE PROFESSIONALS CONCERNED BY HAND HYGIENE

All health-care professionals who are in direct and indirect contact with patients and their surroundings during their respective activities are concerned with hand hygiene. The modes of germ transmission may differ depending on the activity, but the entity of the risk associated with transmission in a particular situation is usually unknown. For this reason, all persons involved in health-care delivery are responsible for halting microbial transmission when direct or indirect contact justifies the indications for hand hygiene. In a care environment, all activities involving direct or indirect contact with patients are considered to be health-care activities. This means that, apart from administrative staff, all health professionals, regardless of the setting, are potentially concerned with hand hygiene during the course of carrying out their duties.

II.3 HEALTH-CARE ACTIVITIES AND INDICATIONS

Health-care activity may be described as a succession of tasks during which health-care workers’ hands touch different types of surface (patient’s hands, mucous membrane, intravenous catheter, bedside table, medical instrument, waste, food, urine). Germ transmission from one surface to another must be interrupted, as each contact may be a potential source of contamination by or to a health-care worker’s hands. Whenever there is a risk of germ transmission, the indications apply during the time window between contacts.

The aim of the indications for hand hygiene are:

1) to interrupt the transmission of germs via the hands (Figure 5): a) between the health-care area and the patient zone; b) between the patient zone and the health-care area; c) to a critical site with infectious risk for the patient (e.g. a mucous membrane, non-intact skin, an invasive medical device); d) from blood and body fluids.

2) to prevent: a) colonization of the patient by potential (including multi-resistant) pathogens; b) dissemination of potential (including multi-resistant) pathogens in the health-care area; c) infections caused mainly by endogenous micro-organisms; d) colonization and infection of health-care workers.

II.4 HAND HYGIENE INDICATIONS AND HAND HYGIENE ACTIONS

The performance of effective hand hygiene involves awareness by health-care workers of the indications and of when and in what order they apply during health-care activities. The hand hygiene action can be performed either by handrubbing with an alcohol-based product or by hand washing with soap and water.

An indication makes hand hygiene necessary at a given moment. It is justified by a risk of germ transmission from one surface to another and each indication is restricted to a specific contact. The indications described here apply to routine care only and not to procedures requiring surgical hand preparation.

The indications for hand hygiene do not correspond to the beginning and end of a sequence of health-care activities. There is an indication for hand hygiene whenever a health-care worker’s hands move from one geographical area to another (from the health-care area to the patient zone and vice versa), from one critical site to another body site on the same patient (for example, from a critical site with body fluid exposure risk to a simple contact with the patient), or away from the patient (for example, from the health-care area to a critical site for the patient).
According to the WHO “My five moments for hand hygiene” approach, the hand hygiene indications recommended by the WHO Guidelines on Hand Hygiene in Health Care merge in five essential moments when hand hygiene is needed within the health-care flow (see table below).

**Table.** Correspondence between the indications and the WHO recommendations

<table>
<thead>
<tr>
<th>The 5 Moments</th>
<th>Consensus recommendations WHO Guidelines on Hand Hygiene in Health Care 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Before touching a patient</td>
<td>D.a) before and after touching the patient (IB)</td>
</tr>
<tr>
<td>2. Before clean/aseptic procedure</td>
<td>D.b) before handling an invasive device for patient care, regardless of whether or not gloves are used (IB)</td>
</tr>
<tr>
<td></td>
<td>D.d) if moving from a contaminated body site to another body site during care of the same patient (IB)</td>
</tr>
<tr>
<td>3. After body fluid exposure risk</td>
<td>D.c) after contact with body fluids or excretions, mucous membrane, non-intact skin or wound dressing (IA)</td>
</tr>
<tr>
<td></td>
<td>D.d) if moving from a contaminated body site to another body site during care of the same patient (IB)</td>
</tr>
<tr>
<td></td>
<td>D.f) after removing sterile (II) or non-sterile gloves (IB)</td>
</tr>
<tr>
<td>4. After touching a patient</td>
<td>D.a) before and after touching the patient (IB)</td>
</tr>
<tr>
<td></td>
<td>D.f) after removing sterile (II) or non-sterile gloves (IB)</td>
</tr>
<tr>
<td>5. After touching patient surroundings</td>
<td>D.e) after contact with inanimate surfaces and objects (including medical equipment) in the immediate vicinity of the patient (IB)</td>
</tr>
<tr>
<td></td>
<td>D.f) after removing sterile gloves (II) or non-sterile gloves (IB)</td>
</tr>
</tbody>
</table>

The concept attempts to go beyond the long list (never exhaustive) of health-care actions and situations requiring hand hygiene; it does not define specific and multiple procedures and care situations but rather helps focus on essential moments embedded within the care sequence that are essential for hand hygiene. The concept does not in any way reduce the need for hand hygiene. It is a tool to identify moments when hand hygiene must be performed as well as to distinguish those when it is not useful.

**II.5 UNDERSTANDING MORE ABOUT APPLYING THE FIVE MOMENTS**

Two of the five moments for hand hygiene occur before contact or health-care procedure; the other three occur after contact or exposure to body fluids. Indications corresponding to the “before” moments indicate the need to prevent the risk of microbial transmission to the patient. The “after” indications are intended to prevent the risk of microbial transmission to the health-care worker and the health-care area (i.e. other patients, their surroundings and the health-care environment). During a sequence of health-care activities, certain indications may coincide at the same moment. If, as a result, only one hand hygiene action is required, the indications must be individually assessed in the light of the expected outcome.

**II.5.1 Indication (moment) 1: Before touching a patient**

**When:** before touching a patient when approaching him/her. This indication is determined by the occurrence of the last contact with the health-care area and the next contact with the patient.

**Why:** to prevent germ transmission from the health-care area to the patient and ultimately to protect the patient against colonization and, in some cases, against exogenous infection by harmful germs carried on health-care workers’ hands.

**Notes:** This moment occurs before contact with the patient’s intact skin and clothing; the hand hygiene action can be performed either while entering the patient zone, when approaching the patient, or immediately before touching him/her. Contact with surfaces in patient surroundings may occur by touching items between the time of entering the patient zone and the contact with the patient; hand hygiene is not required before touching these surfaces but before contact with the patient. If, following hand hygiene but before an “initial” contact with the patient, other contacts of the same kind or with patient surroundings occur, then hand hygiene does not need to be repeated.
Situations illustrating direct contact:
- before shaking hands with a patient, stroking a child’s forehead;
- before assisting a patient in personal care activities: to move, to take a bath, to eat, to get dressed, etc;
- before delivering care and other non-invasive treatment: applying oxygen mask, giving physiotherapy;
- before performing a physical, non-invasive examination: taking pulse, blood pressure, chest auscultation, recording ECG.

Why: to prevent germ transmission to the patient and from one body site to another in the same patient through inoculation.

Notes:
If gloves are used to perform the clean/aseptic procedure, hand hygiene must be performed before they are donned.
The indication is not defined by a sequence of health-care actions but instead by direct or indirect contact with mucous membranes, damaged skin or an invasive medical device.
Any health-care worker operating “upstream” from actual direct care and preparing an item meant to be in contact with mucous membranes or non-intact skin through ingestion or inoculation (sterilization worker, pharmacist, cook) must also consider this indication.

Situations illustrating clean/aseptic procedures:
- before brushing the patient’s teeth, instilling eye drops, performing a digital vaginal or rectal examination, examining mouth, nose, ear with or without instrument, inserting suppository/pessary, suctioning mucous;
- before dressing a wound with or without instrument, applying ointment on vesicle, performing a percutaneous injection/puncture;
- before inserting an invasive medical device (nasal cannula, nasogastric tube, endotracheal tube, urinary probe, percutaneous catheter, drainage), disrupting/opening any circuit of an invasive medical device (for food, medication, draining, suctioning, monitoring purposes);
- before preparing food, medications, pharmaceutical products, sterile material.

Why: immediately before accessing a critical site with infectious risk for the patient. This indication is determined by the occurrence of the last contact with any surface in the health-care area and in the patient zone (including the patient and his/her surroundings), and any procedure involving any direct and indirect contact with mucous membranes, non-intact skin or an invasive medical device.

Notes:
The indication is not defined by a sequence of health-care actions but instead by direct or indirect contact with mucous membranes, damaged skin or an invasive medical device.
Any health-care worker operating “upstream” from actual direct care and preparing an item meant to be in contact with mucous membranes or non-intact skin through ingestion or inoculation (sterilization worker, pharmacist, cook) must also consider this indication.
II.5.3 Indication (moment) 3: After body fluid exposure risk

When: as soon as the task involving exposure risk to body fluids has ended (and after glove removal). This indication is determined by the occurrence of contact (even if minimal and not clearly visible) with blood or another body fluid and the next contact with any surface, including the patient, the patient surroundings or the health-care area.

Why: To protect the health-care worker from colonization or infection with the patient’s germs and to protect the health-care environment from germ contamination and potential subsequent spread.

Notes: If the health-care worker is wearing gloves at the time of exposure to a body fluid, they must be removed immediately thereafter and hand hygiene must be performed. This action may be postponed until the health-care worker has left the patient surroundings if the health-care worker has to remove and process equipment (e.g. an abdominal drainage tube) on appropriate premises, and provided that he or she only touches this equipment before performing hand hygiene.

Any health-care worker operating “downstream” from the actual direct patient care and involved in handling body fluids (laboratory technician, pathologist), contaminated and soiled equipment (sterilization worker), contaminated and soiled waste (maintenance or utility worker) must also consider this indication.

Situations illustrating body fluid exposure risk:

a) when the contact with a mucous membrane and/or with non-intact skin ends;

b) after a percutaneous injection or puncture ends; after inserting an invasive medical device (vascular access, catheter, tube, drain, etc); after disrupting and opening an invasive circuit;

c) after removing an invasive medical device;

d) after removing any protection (napkin, dressing, gauze, sanitary towel, etc);

e) after handling an organic sample; after clearing excreta and any other body fluid; after cleaning any contaminated surface and soiled material (soiled bed linen, dentals, instruments, urinal, bedpan, lavatories, etc).

Practical example:

<table>
<thead>
<tr>
<th>Risk of exposure to a body fluid which justifies indication 3</th>
<th>Indication 3 After exposure risk to body fluid</th>
<th>Contact occurs with the patient, his/her surroundings or care environment following indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>The health-care worker changes soiled sheets and removes a bedpan from a bed-bound patient, places sheets in a bag and removes gloves.</td>
<td>The health-care worker performs hand hygiene.</td>
<td>The health-care worker helps patient back into bed.</td>
</tr>
</tbody>
</table>

II.5.4 Indication (moment) 4: After touching a patient

When: when leaving the patient’s side, after having touched the patient. This indication is determined by the occurrence of the last contact with intact skin or the patient’s clothing or a surface in the patient’s surroundings (following contact with the patient), and the next contact with a surface in the health-care area.
**Why:** to protect the health-care worker from colonization and potential infection by patient germs and to protect the environment in the health-care area from germ contamination and potential spread.

**Notes:** The action may be postponed until the health-care worker has left the patient zone if the health-care worker has to remove and process equipment on appropriate premises, and provided that he or she touches this equipment only before performing hand hygiene. Indication 4 cannot be dissociated from indication 1. When the health-care worker touches the patient directly and then touches another object in the patient surroundings before leaving the zone, indication 4, and not 5, applies.

**Indication 4** cannot be dissociated from indication 1. When the health-care worker touches the patient directly and then touches another object in the patient surroundings before leaving the zone, indication 4, and not 5, applies.

**Practical example:**

<table>
<thead>
<tr>
<th>Contact with the patient and/or his or her surroundings which justifies indication 4</th>
<th>Indication 4 After touching a patient</th>
<th>Contact with environment in the health-care area which follows indication 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>The health-care worker helps the patient to sit back in the bed.</td>
<td>The health-care worker performs hand hygiene action.</td>
<td>The health-care worker answers the telephone.</td>
</tr>
</tbody>
</table>

**II.5.5 Indication (moment) 5: After touching patient surroundings**

**When:** after touching any object or furniture when leaving the patient surroundings, without having touched the patient. This indication is determined by the occurrence of the last contact with inert objects and surfaces in the patient surroundings (without having touched the patient) and the next contact with a surface in the health-care area.

**Why:** To protect the health-care worker against colonization by patient germs that may be present on surfaces/objects in patient surroundings and to protect the health-care environment against germ contamination and potential spread.

**Note:** Indication 4, “after touching a patient” and indication 5 “after touching patient surroundings” may never be combined, since indication 5 excludes contact with the patient and indication 4 applies only after patient contact.

**Situations illustrating contacts with patient surroundings:**

a) after a maintenance activity: changing bed linen with the patient out of the bed, holding a bed rail, clearing a bedside table;

b) after a care activity: adjusting perfusion speed, clearing a monitoring alarm;

c) after other contacts with surfaces or inanimate objects (that should ideally be avoided): leaning against a bed, a night table.

**Practical example:**

<table>
<thead>
<tr>
<th>Contact with inert objects and surfaces in patient surroundings which justifies indication 5</th>
<th>Indication 5 After contact with patient’s surroundings</th>
<th>Contact with care environment which follows indication 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>The health-care worker has removed the sheets of the unoccupied bed and has discarded them in a bag.</td>
<td>The health-care worker performs hand hygiene.</td>
<td>The health-care worker answers the telephone.</td>
</tr>
</tbody>
</table>
II.5.6 Understanding the five moments within the care sequence

The sequence of health-care actions delivered to a single patient or to several patients can lead to a number of hand hygiene indications occurring simultaneously. This does not mean that each indication requires a separate hand hygiene action. One hand hygiene action is justified by the indication that immediately precedes or follows a sequence of two or more contacts; a single hand hygiene action is enough to prevent all risk of microbial transmission.

Figure 7 illustrates an example of the coincidence of two indications: when a health-care worker moves from one patient to another, which would normally imply different indications depending on the point of view of each patient. Indication 4, in this case “after touching patient A”, applies when he or she leaves patient A to attend to patient B; and indication 1, “before touching patient B”, applies in this case before contact occurs between the health-care worker and patient B. There are a number of other situations where more than one indication coincide. Innumerable combinations are possible for all indications, except for 4 and 5.
II.6 INDICATIONS FOR HAND HYGIENE WHEN MEDICAL GLOVES ARE REQUIRED

The indications for hand hygiene are independent of those that justify the use of gloves (whether sterile or non-sterile). Glove use neither alters nor replaces the performance of hand hygiene: a) where an indication for hand hygiene precedes a task involving contact that necessitates the use of gloves, hand hygiene must be performed before donning gloves; b) where an indication follows a task involving contact that requires the use of gloves, hand hygiene must be performed after the gloves are removed; c) where an indication occurs while the health-care worker is wearing gloves they must be removed to allow hand hygiene performance and, if necessary, changed. The use of gloves does not determine indications for hand hygiene; rather, hand hygiene influences the appropriate use of gloves.

For extensive information about glove use, refer to the “Glove use information leaflet” included in the Implementation Package of the WHO Multimodal Hand Hygiene Improvement Strategy.

In summary

Hand hygiene indications can be merged into five moments during health-care delivery. Knowing, understanding and recognizing these moments are the pillars on which effective hand hygiene is based. If health-care workers promptly identify these indications (moments) and respond to them by complying with hand hygiene actions, it is possible to prevent health care-associated infections caused by cross-transmission via hands. The right action at the right moment is a guarantee of safe patient care.
III.1. THE PURPOSE OF OBSERVATION

The main purpose of observation is to demonstrate the degree of compliance with hand hygiene among health-care workers and, in some cases, to assess the type and quality of the technique used to perform it. Depending on the level of compliance by health-care workers and the type of setting, and in accordance with specific priorities, the results of the observation also help determine the most appropriate interventions for hand hygiene promotion, education and training. Conducting observations before and after such a period of intervention makes it possible not only to evaluate hand-hygiene compliance levels repeatedly but also to measure improvements and the impact of the intervention, and adjust education material and campaigns.

If available, the results of the observation can be correlated with the trends of HCAI rates, the indicator for evaluating the outcome of a hand hygiene promotion strategy.

The main purpose of the WHO method for direct observation proposed here is to produce large-scale data on compliance with hand hygiene in the most accurate way and according to the “My five moments for hand hygiene” approach.

III.2. DIRECT OBSERVATION OF HAND HYGIENE PRACTICES

Direct observation of health-care workers while delivering routine care is one of the methods to evaluate hand hygiene practices. A direct observation method is chosen because it generates the most accurate data on health-care workers’ compliance with the recommendations on hand hygiene, although the results should not be regarded as a perfect representation of the actual situation. Its advantages are: a) the real-time denominator allows results simultaneously relating to time, place and circumstances to be compared; and b) consistency between the reference concepts, definitions and tools used by both health-care workers and observers. The two main disadvantages of the method are the potential influence the observer may have on the behaviour of health-care workers (since this method implies that the health-care worker is aware of being observed), and the impact of the observer’s interpretation of the definitions and the actual situation on the reliability of the data.

III.3. THE RULES OF OBSERVATION

Usually it is recommended that observation data be collected anonymously and kept confidential. The results of observations should not be employed to carry out administrative evaluation of staff. However in some cases, by institutional decision or because there is no specific obstacle to health-care workers’ identification, individual observation including health-care worker identification may be undertaken also for educational purposes. Indeed, to improve understanding of hand hygiene and to contribute to its promotion, wherever possible the results of an observation should be presented immediately to the health-care staff who have been observed (performance feedback). This should be done in a way that allows an exchange of views conducive to fostering a safety culture and trust among those who have taken part.

For example, feedback can be given in meetings or else to individuals at a convenient time during their working day in a simple written format that can be posted in a convenient place in a clinical setting and discussed on an on-going basis and compared to future compliance information. In addition, final results should be sent to all the concerned health-care workers either collectively or individually as well as to others, for example management or infection control committees according to local decisions. This should occur as soon as the data has been collected as possible. Observation is a way of making health-care staff aware of the need to practise hand hygiene: simply observing hand hygiene practices, providing feedback and commenting on the results has an immediate promotional effect. Thus, in conditions where overall baseline compliance should be assessed, feedback should not be given until overall ratios are estimated (i.e. the expected total number of opportunities for hand hygiene has been observed, see Section III.8).

III.4. THE OBSERVER AND HIS/HER ROLE

The primary role of the observer is openly and objectively to observe practices and to gather data on hand hygiene using the five indications along with the methodology and instructions proposed here. Before doing so, observers must be familiar with the five indications and their underlying concepts, which they must be able to apply, identify, differentiate and explain. Although the basic knowledge of hand hygiene required is summarized in this reference manual, the observer should have previous broad experience of patient care and clinical
management in order to be able to translate the concepts into practice. However, as an observer he/she must also be able to carry out the observational duties objectively. The observers’ positions vest them with a reference role, both for the persons observed and for administrative and decision-making staff. Usually they are also responsible for promoting and in some cases teaching hand hygiene, providing feedback and commenting on the results, and for helping shape the campaign in accordance with the needs of the health-care workers. The observer must, therefore, have knowledge and understanding of how a promotional campaign is carried out.

The observer introduces himself or herself at a convenient time to the health-care workers to be observed and to the patients (if applicable), and provides a general explanation for his or her presence (for example, observation of health-care practices). It is recommended that the period of observation be formally announced to the head nurse and chief doctor of the unit; in some settings written permission by the patients will be required. Health-care workers should be made aware whether observation is anonymous or not and of the way the collected information will be used. Respect for patients’ privacy must always be reflected in the observer’s behaviour, which should not interfere with health-care activities being carried out during the session. Observation should not be performed in extreme situations (emergency medical treatment, signs of uncontrolled stress in a health-care worker being observed) as they do not reflect a “standard” care situation. The observer must be able to withdraw from such a situation. However, this does not preclude observation in emergency and intensive care wards.

The observer usually stands close to the point of care. While observing, it is advisable to place a solid backing under the form to make it easier to fill in. It is also easier to make corrections if a pencil and eraser are used; however, observers should constantly be aware of their need for objectivity and not change recording inputs unless an absolute error in observation has been made. A watch should be used for timing sessions. However, if the observer uses a wrist watch, he or she should set a good example by not wearing it on his or her wrist and by refraining from wearing other jewellery. Nails should be short and unvarnished, and false nails should not be worn as per all health-care practices. Observers must always be careful not to make assumptions when identifying an indication, it is not counted as an opportunity and no action corresponding positive or negative action. A positive action indicates compliance; a negative action indicates non-compliance. A positive action that is not justified by an identified indication that therefore cannot be translated into an opportunity cannot be included when measuring compliance.

The chronology of events may be variable: the indication may precede (after body fluid exposure risk, after touching patient or after touching patient surroundings) or follow (before touching patient or before clean/aseptic task) the hand hygiene action. Recording an indication at a given moment does not exclude the possibility of combining other indications with it provided that the sequence of activities is adhered to and that there are corresponding positive hand hygiene actions. For example, a health-care worker enters the patient surroundings, performs hand hygiene (indication 2) and connects an intravenous infusion fixed to a three-way stopcock (without touching the patient). Once the procedure has been completed, the health-care worker takes the patient’s pulse (indication 1). The performance of hand hygiene before the clean/aseptic task (indication 2) is also “valid” for indication 1, which follows.

The main focus of the observation should not be primarily the action but rather the identification of the indication to which the health-care worker then responds positively or negatively, either before or after the contact that determines the indication. Quite simply, if the observer identifies one or more indications, it is counted as an opportunity and either a positive or negative action is recorded. If the observer does not identify an indication, it is not counted as an opportunity and no action is recorded. The connection between indication, opportunity and action is illustrated in Figure 8.

III.6. HAND HYGIENE ACTION SEEN BY THE OBSERVER

The observer should always establish a link between an observed hand hygiene action and an accounted opportunity. The action may be either negative (not performed) or positive (performed). In some cases the action may not be capable of being seen by the observer, so the observer should record only actions that he or she can clearly see and that correspond to indications; the observer is not allowed to assume that an action has taken place. The moment the observer identifies an indication, it is counted as an opportunity to which there should be a corresponding positive or negative action. A positive action indicates compliance; a negative action indicates non-compliance. A positive action that is not justified by an identified indication that therefore cannot be translated into an opportunity cannot be included when measuring compliance.

III.5 THE OPPORTUNITIES FOR HAND HYGIENE

The basic references and definitions used by observers to identify hand hygiene actions during health-care activities are identical to those listed in Section II.5 and apply equally to hand hygiene observation, training and practice. However, observers have a different perspective on the indications and actions from health-care workers and trainers. When an indication is identified by the observer, he or she converts it into an opportunity while recording it, using a special accounting procedure. The opportunity determines the need to perform the hand hygiene action, whether the reason (the indication that leads to the action) is single or multiple. From the observer’s point of view, the opportunity exists whenever one of the indications for hand hygiene occurs and is observed. Several indications may arise simultaneously, creating a single opportunity and requiring a single hand hygiene action (see Section II.5.6). The opportunity is an accounting unit equivalent to the number of hand hygiene actions required, regardless of the number of indications. Compliance is measured by dividing the number of actions (the numerator) by the number of opportunities (the denominator) (see Section III.7).
According to Figure 8, during the observation of health-care activities in a given time x, the observer:

- identified nine indications;
- counted six opportunities: 1, 4 and 6 are each defined by two indications (a and b, e and f, as well as h and i);
- observed four positive (performed) hand hygiene actions of which three are linked to opportunities 1, 4 and 6; one observed action had no link to any opportunity;
- observed three negative actions (not performed) linked to opportunities 2, 3 and 5.

In addition, the observer should not record indications for hand hygiene arising from habitual or unconscious actions by the health-care worker during their duties, such as adjusting spectacles or pushing back a strand of hair. The fact that they are unconscious means they cannot be recorded as indication for hand hygiene. An exception, which must be counted, is when the performance of a habitual action leads to the interruption of a sterile procedure.

### III.7. REPORTING HAND HYGIENE COMPLIANCE

When reporting data on hand hygiene practices, the observer must always bear in mind the following:

- at least one indication for hand hygiene must be observed to define an opportunity;
- each opportunity requires one hand hygiene action;
- one action may apply to more than one indication;
- a documented action may be either positive or negative provided it corresponds to an opportunity;
- observation of a positive action does not always imply the existence of an opportunity.

Compliance with hand hygiene is the ratio of the number of performed actions to the number of opportunities and is expressed by the following formula:

\[
\text{Compliance (\%)} = \frac{\text{Performed actions}}{\text{Opportunities}} \times 100
\]

This reflects the degree of compliance by health-care workers with the requirement to practise hand hygiene during health-care activities in line with the five indications (moments) as they are counted as opportunities. Compliance describes an exact equivalence between the number of actions and the number of opportunities. Non-compliance is when the number of opportunities exceeds the number of actions performed.

### III.8. OBSERVATION METHODOLOGY

The reliability and impartiality of the data collected, which should accurately reflect the situation observed, will depend on the methodology developed and its implementation.

First, the scope of observation – setting, professional categories and indications – must be defined. According to the WHO multimodal hand hygiene improvement strategy, observation should take place in areas where the strategy is being, or will be, implemented: one or more health-care units/wards, one or more medical departments or the entire health-care facility. According to the methodology described here, only health-care workers in direct contact with patients are objects of observation, which in no way means that other health-care workers are excluded from performing hand hygiene (see Section II.3).

Health-care workers are divided into four broad professional categories: 1) nurse/midwife; 2) auxiliary; 3) medical doctor and 4) other health-care workers. Each category may be subdivided in accordance with the information required. Either all or some of the professional categories can be chosen for observation. The main requirement is that they should be representative in terms of professional category and setting. For example, if 50% of the workforce in a given setting is nurses then 50% of the professional category being observed should be nurses. If the scope of the observation covers the whole health-care facility and all the health-care workers, all the medical services and all the professional categories must be represented in the observational data.

The observation period is defined as the time window during which compliance is measured in a certain setting. The length of the period will depend on the sample size. When comparing hand hygiene compliance during two different periods (e.g. before and after hand hygiene promotion), the sample size should be adjusted to ensure comparability.
size should be large enough to exclude the influence of chance. Ideally, a sample size calculation should therefore be performed at the stage of designing the hand hygiene monitoring scheme. There is no clear evidence on the ideal sample size needed to ensure representativeness, but sample size estimates indicate that 200 opportunities per observation period and per unit of observation (either ward, department, or professional category etc) are needed to compare results reliably. Figure 9 shows examples of sample size calculations according to estimates of baseline and follow-up compliance levels.

Figure 9. Sample size (number of opportunities) according to expected hand hygiene compliance increase of 10% or 20%


Depending on the size of the observation, a representative sample may be obtained either by randomization or by systematic observation. If it has been decided to observe nurses in a single health-care unit, each member of that category must be systematically observed. If the observation instead covers all the health-care workers in a medical department employing some 500 professionals, preferably randomization should be used. To do this, the methodology proposes sequencing the observation in sessions of limited duration, with each session being conducted in a different setting, with different health-care workers and at different times. This will generally ensure a representative sample. To allow comparison between data collected in different observation periods, the methods for determining the sampling should be similar.

The observation session is the time when the observation takes place in a defined setting (ward). It is numbered and timed (start and end times) in order to calculate its total duration. The time set for the duration should be about 20 minutes (+10 minutes) depending on the activity being observed. As far as possible, it is preferable for a health-care sequence to be observed from beginning to end. For this reason, the session may be extended if necessary. If the observed health-care workers need to interrupt their activity with patients while the observation is under way, it is preferable to terminate the session. Finally, if during the session no relevant health-care activity is observed, it would be pointless to prolong it.

The purpose of breaking down the observation into sessions in this way is to acquire an overview of practices (different health-care workers working in different places).

The methodology described here enables either an unlimited number of health-care workers in all four professional categories mentioned above to be observed either during a single session or a number limited up to four individuals per session. The former option, i.e. the larger sample, has the advantage of allowing the most rapid, large-scale collection of the greatest number of opportunities, even in settings where the intensity of activity is limited; its disadvantage is that it is not possible to collect and identify data at the individual level. On the other hand, by focusing on no more than four health-care workers it is possible to obtain information at the individual level and to identify the health-care worker even though it takes longer to collect the data.

The aim of the method proposed here is to generate data on compliance with hand hygiene on a large scale. It can easily be
modified nonetheless to suit specific local situations without changing the underlying principles that are based on the detection of the five moments for hand hygiene promoted by WHO. The method can be adapted according to the professional category and indication (i.e. only some categories can be observed and/or compliance with certain and not all of the five indications be detected). In addition, other items linked to the observational data may be incorporated without necessitating any fundamental change; for example the connection between the use of gloves and non-compliance with hand hygiene. In this case, when glove use is observed in parallel with a negative hand hygiene action (not performed), the information should be systematically recorded. The inclusion of such data enables to measure the impact of glove use on non-compliance. This information should not be confused with monitoring glove usage.

To sum up, the following principles must always be adhered to:

- define the scope of the observation
- gather data on 200 opportunities per observation per unit (either ward, department or professional category, etc) per observation period;
- observe practices by health-care professionals in direct contact with patients;
- document the data by professional category and by setting, gathered during 20 minute sessions (may be up to 10 minutes longer or shorter);
- do not observe more than three health-care workers simultaneously.

III.8.1 The Observation Form

The Observation Form (Appendix, pp. 1 and 2) contains a framework for conducting observations. It consists of two elements: a header and a corresponding grid.

**Figure 10. The header**

<table>
<thead>
<tr>
<th>Facility:</th>
<th>Period Number*:</th>
<th>Session Number*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Service:</td>
<td>Date: (dd/mm/yy)</td>
<td>/ / Observer: (initials)</td>
</tr>
<tr>
<td>Ward:</td>
<td>Start/End time: (hh:mm)</td>
<td>/ / Page N°:</td>
</tr>
<tr>
<td>Department:</td>
<td>Session duration: (mm)</td>
<td>Country**:</td>
</tr>
<tr>
<td>City**:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The header (Figure 10) allows observations to be precisely located in time and place (setting, date, session duration and observer) and the data to be classified and recorded (period, session). This information must be entered before the observational data is recorded in order to ensure that the latter are eligible for use in the analysis.

According to the scale of the observation, the local institutional nomenclature system for naming the facility, the service, the ward and the department should be used to complete the header. The WHO codes can also be used, allowing data comparison from different institutions worldwide. These are: 1) medical (including dermatology, neurology, haematology, oncology, etc.); 2) surgical (including neurosurgery, urology, ENT, ophthalmology, etc.); 3) mixed (medical and surgical, including gynaecology); 4) obstetrics (including related surgery); 5) paediatrics (including related surgery); 6) intensive care and resuscitation; 7) emergency; 8) long-term care and rehabilitation; 9) ambulatory (including related surgery) and 10) other (to be specified).

Locating the observation in time allows the period of evaluation to be defined and dated in relation to interventions (before and after an intervention, follow-up, etc.).

Indicating the time when a session begins and ends allows its duration to be defined and compliance to be evaluated in relation to the intensity of hand hygiene opportunities during a given time. To conduct observation in sessions ensures, inter alia, that a range of settings, professional categories and hand hygiene moments are observed.
By inserting his or her initials in the Observation Form, the observer indicates that it has been checked before being returned. It also allows data to be verified and any sign of bias on the part of the observer to be identified. Each session is allocated a number to indicate that the data are ready to be analysed. This number is entered in a database when the data are processed as well as in the Basic Compliance Calculation. The page number only needs to be entered if more than one form is used during a single session.

Figure 11. The grid

<table>
<thead>
<tr>
<th>Prof.cat</th>
<th>Prof.cat</th>
<th>Prof.cat</th>
<th>Prof.cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code</td>
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<td>Code</td>
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<tr>
<td>N°</td>
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<td>1</td>
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<td></td>
<td>bef-pat.</td>
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<td>bef-b.f.</td>
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</table>

The data observation grid (Figure 11) contains the data needed to measure compliance. It is divided into four columns; the column can be dedicated either to a professional category (in this case different health-care workers of that category are recorded in the column) or to an individual health-care worker whose category is mentioned. Where data are classified by professional category, the number of health-care staff observed in each category during each session must be specified. There is no upper limit. Where data are classified by health-care worker, a maximum of four can be included in the same form.

Health-care workers are classified in the following categories and using codes as follows:

1. nurse/midwife
   1.1 nurse
   1.2 midwife
   1.3 nurse/midwife student
2. auxiliary
3. medical doctor
   3.1 in internal medicine
   3.2 surgeon,
   3.3 anaesthetist/resusciator/emergency physician
   3.4 paediatrician
   3.5 gynaecologist
   3.6 consultant
   3.7 medical student
4. other health-care worker
   4.1 therapist (physiotherapist, occupational therapist, audiologist, speech therapist, etc)
   4.2 technician (radiologist, cardiology technician, operating room technician, laboratory technician, etc)
   4.3 other (dietician, dentist, social worker, other care professional)
   4.4 student

Each column (Figure 12) is independent of the others: the chronology of the data does not have to be the same in each column. It depends on the number of opportunities observed for each professional category or for each individual. Several health-care workers may be observed at the same time (when they are working with the same patient or in the same room); however, it is not advisable to observe more than three health-care workers simultaneously. Depending on the intensity of activities and indications, observers should limit the observation to one or two health-care workers so as to preclude the possibility of missing opportunities during a care sequence. The observer must always be able to capture and record all the indications that apply to the activities and to the health-care workers observed.

Each column contains eight boxes. Each box corresponds to an opportunity where the indications and the positive or negative actions observed are entered. The square box in the form (□) means that no item is exclusive (if several items apply to the opportunity, they should all be marked); the circle (○) means that a single item applies to the opportunity and concerns negative hand hygiene actions (zero action) as well as information on glove use, if recorded.

A positive hand hygiene action is reported according to the method used: either by rubbing with an alcohol-based handrub, or washing with soap and water, or a combination of both in that order. According to this method, the quality of the performance is not evaluated (technique, time). Where a positive action is recorded without a corresponding indication, it should not be counted when data are analyzed. A negative hand hygiene action must be recorded so that the opportunity may be included in the analysis. The data grid employs the following abbreviations for the five hand hygiene indications: bef.pat: before touching a patient; bef.aspt: before clean/aseptic procedure; aft.b.f: after body fluid exposure risk; aft.pat: after touching
**III.8.2 Basic Compliance Calculation**

This form (Appendix, pp. 3 and 4) is particularly recommended for use by health-care facilities that do not have information technology tools for collecting and analysing electronic data. The tool is designed to produce global compliance results broken down by professional category and indication. However, it may also be used to subdivide the results by setting.

Compliance with hand hygiene is the ratio of the number of performed actions to the number of opportunities as expressed by the following formula:

\[
\text{Compliance (\%)} = \frac{\text{Performed actions}}{\text{Opportunities}} \times 100
\]

On the Observation Form, the indications observed are classified as opportunities for hand hygiene (the denominator), against which the positive hand hygiene action is set (the action serving as the numerator).

Results for compliance may be calculated globally but also broken down by professional category and setting. Thus when health-care workers receive the data, they can refer to their professional category or setting.
The form for basic calculation of compliance per professional category is shown below.

**Figure 13.**

<table>
<thead>
<tr>
<th>Session n°</th>
<th>Opp (n)</th>
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<th>HW (n)</th>
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<th>HW (n)</th>
<th>HR (n)</th>
<th>Total per session</th>
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</table>

The total number of opportunities for each session, together with the total number of positive actions performed (rubbing or washing with soap and water) are entered. Each numbered line corresponds to the results of one session; the corresponding number is entered in the form to verify that the relevant data has been included when measuring compliance. The grid allows the results to be broken down by professional category and/or location. Compliance is calculated by adding up the results of each session and dividing the total number of positive actions by the total number of opportunities. From these calculations, the proportion of positive actions of handrubbing with an alcohol-based product or hand washing with soap and water can be extracted and put in relation to other aspects, notably the infrastructure available for hand hygiene.

Overall compliance with hand hygiene for each professional category and setting can also be calculated according to the five indications. This is not an accurate measurement of compliance, however, since indications do not constitute a completely reliable denominator, but the results give some idea of how health-care workers perform hand hygiene. The results reflect the connection between positive actions where hands are rubbed with an alcohol-based product or washed with soap and water and the indication for hand hygiene. Where several indications coincide in a single opportunity, each indication is recorded and the associated positive action is then multiplied by the number of indications.
The form for basic calculation of compliance per indication is shown below.

Figure 14.

<table>
<thead>
<tr>
<th>Facility:</th>
<th>Period:</th>
<th>Setting:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before touching a patient</td>
<td>Before a clean/aseptic procedure</td>
<td>After body fluid exposure risk</td>
</tr>
<tr>
<td>After body fluid exposure risk</td>
<td>After touching a patient</td>
<td>After touching patient surroundings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session n°</th>
<th>Indic (n)</th>
<th>HW (n)</th>
<th>HR (n)</th>
<th>Indic (n)</th>
<th>HW (n)</th>
<th>HR (n)</th>
<th>Indic (n)</th>
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<th>HR (n)</th>
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<th>HW (n)</th>
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</table>

Calculation:

\[
\text{Act (n)} = \frac{\text{Indic1 (n)}}{\text{Act (n)}} = \frac{\text{Indic2 (n)}}{\text{Act (n)}} = \frac{\text{Indic3 (n)}}{\text{Act (n)}} = \frac{\text{Indic4 (n)}}{\text{Act (n)}} = \frac{\text{Indic5 (n)}}{\text{Act (n)}},
\]

Ratio Act/Indic

Similar to the basic compliance calculation per professional category, the total number of opportunities and positive actions is reported for each session. When carrying out an observation, constant vigilance is needed in order to avoid missing a connection between an indication and an action, which may occur at random during a session and is not specifically catered for in the form. Establishing a correlation between indications and actions enables education and training programmes for health-care workers to be designed on the basis of the observed behaviour as well as in light of the overall picture generated by the indications. While presenting results on hand hygiene in this way it is assumed that the people concerned know about the indications (definitions, transmission risk, examples), but it also provides initial support for the implementation of training measures to develop such knowledge.
IV.1 HAND SAFETY

Skin underneath jewellery rings is more heavily colonized by germs than comparable areas of skin on fingers without rings; therefore wearing jewellery encourages the presence and survival of transient flora. The consensus recommendation is strongly to discourage the wearing of rings or other jewellery during health care.

The areas above and below nails attract germs, particularly if nails are long, varnished or if false nails are worn. Wearing artificial nails may contribute to the transmission of certain healthcare-associated pathogens.

Any changes in the superficial layer of the epidermis and deeper damage also encourage colonization by non-commensal skin flora (e.g. *Staphylococcus aureus* and Gram negative bacteria).

Ensuring hand safety by not wearing jewellery, keeping nails short and caring for the skin are other aspects of hand hygiene that enhance the efficacy of handrubbing with an alcohol-based handrub and washing with soap and water.

IV.2 HAND SKIN CARE

Frequent and repeated use of hand hygiene products, particularly soaps and other detergents, may cause irritant contact dermatitis among health-care workers, particularly in settings with intensive care activity where hand hygiene action is required many times per hour as well as during the winter season. Therefore, hand care that includes the regular use of good quality creams and the adoption of appropriate behaviours is of utmost importance to prevent skin damage.

Certain hand hygiene practices can increase the risk of skin irritation and should be avoided. For example, washing hands regularly with soap and water immediately before or after using an alcohol-based product is not only unnecessary, it may lead to dermatitis. Additionally, donning gloves while hands are still wet from either washing or applying alcohol increases the risk of skin irritation. Therefore, certain types of behaviour should be avoided and health-care workers should ensure that their hands are in good condition. Skin tolerability should be considered as one the most important criteria for the selection of a product.
PART V
SELECTED REFERENCE LIST


## Observation Form

### Facility:

Period Number:

Session Number:

### Service:

Date (dd/mm/yy):

Observer (initials):

### Ward:

Start/End time (hh:mm):

Page N°:

### Department:

Season duration (mm):

Country:

### ProCat

<table>
<thead>
<tr>
<th>Code</th>
<th>Code</th>
<th>Code</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

### ProtCat

<table>
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<th>HW</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

### Opposition

<table>
<thead>
<tr>
<th>HH Action</th>
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</table>

### Opp.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Opp. Indication</th>
</tr>
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<tr>
<td></td>
<td></td>
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</tbody>
</table>

### Observation Form

- To be completed by the data manager.
- Optional, to be used if appropriate, according to the local needs and regulations.

---

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WHO acknowledges the Hôpitaux Universitaires de Genève (HUG), in particular the members of the Infection Control Programme, for their active participation in developing this material.
General Recommendations
(refer to the Hand Hygiene Technical Reference Manual)

1. In the context of open and direct observations, the observer introduces him/herself to the health-care worker and to the patient when appropriate, explains his/her task and proposes immediate informal feed back.
2. The health-care worker, belonging to one of the main four following professional categories (see below), is observed during the delivery of health-care activities to patients.
3. Detected and observed data should be recorded with a pencil in order to be immediately corrected if needed.
4. The top of the form (header) is completed before starting data collection (excepted end time and session duration).
5. The session should last no more than 20 minutes (± 10 minutes according to the observed activity); the end time and the session duration are to be completed at the end of the observation session.
6. The observer may observe up to three health-care workers simultaneously, if the density of hand hygiene opportunities permits.
7. Each column of the grid to record hand hygiene practices is intended to be dedicated to a specific professional category. Therefore numerous health-care workers may be sequentially included during one session in the column dedicated to their category. Alternatively each column may be dedicated to a single health-care worker only of whom the professional category should be indicated.
8. As soon as you detect an indication for hand hygiene, count an opportunity in the appropriate column and cross the square corresponding to the indication(s) you detected. Then complete all the indications that apply and the related hand hygiene actions observed or missed.
9. Each opportunity refers to one line in each column; each line is independent from one column to another.
10. Cross items in squares (several may apply for one opportunity) or circles (only a single item may apply at one moment).
11. Performed or missed actions must always be recorded within the context of an opportunity.
12. Performed or missed actions must always be registered within the context of an opportunity.
13. Glove use may be recorded only when the hand hygiene action is missed while the health-care worker is wearing gloves.

Short description of item

<table>
<thead>
<tr>
<th>Facility:</th>
<th>To complete according to the local nomenclature</th>
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</thead>
<tbody>
<tr>
<td>Service:</td>
<td>To complete according to the local nomenclature</td>
</tr>
<tr>
<td>Ward:</td>
<td>To complete according to the local nomenclature</td>
</tr>
<tr>
<td>Department:</td>
<td>To complete according to the following standardized nomenclature:</td>
</tr>
<tr>
<td>Medical, including dermatology, neurology, haematology, oncology, etc., surgery, including neurosurgery, urology, ENT, ophthalmology, etc., mixed (medical &amp; surgical), including gynaecology obstetrics, including related surgery paediatrics, including related surgery intensive care &amp; resuscitation emergency unit long term care &amp; rehabilitation ambulatory care, including related surgery other (to specify)</td>
<td></td>
</tr>
<tr>
<td>Period N°:</td>
<td>1) pre- / 2) post-intervention; and then according to the institutional counter.</td>
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<tr>
<td>Date:</td>
<td>day (dd) / month (mm) / year (yy)</td>
</tr>
<tr>
<td>Start/end time:</td>
<td>hour (hh) / minute (mm).</td>
</tr>
<tr>
<td>Session duration:</td>
<td>Difference between start and end time, resulting in minutes of observation.</td>
</tr>
<tr>
<td>Session N°:</td>
<td>Attributed at the moment of data entry for analysis.</td>
</tr>
<tr>
<td>Observer:</td>
<td>Observer’s initials (the observer is responsible for the data collection and for checking their accuracy before submitting the form for analysis.</td>
</tr>
<tr>
<td>Page N°:</td>
<td>To write only when more than one form is used for one session.</td>
</tr>
<tr>
<td>Prof.cat:</td>
<td>According to the following classification: 1.1  nurse / midwife 1.2  midwife, 1.3  student. 2. auxiliary 3. medical doctor 3.1  in internal medicine, 3.2  surgeon, 3.3  anaesthetist / resuscitator / emergency physician, 3.4  paediatrician, 3.5  gynaecologist, 3.6  consultant, 3.7  medical student. 4. other health-care worker 4.1  therapist (physiotherapist, occupational therapist, audiologist, speech therapist), 4.2  technician (radiologist, cardiology technician, operating room technician, laboratory technician, etc), 4.3  other (dietician, dentist, social worker and any other health-related professional involved in patient care), 4.4  student.</td>
</tr>
<tr>
<td>Number:</td>
<td>Number of observed health-care workers belonging to the same professional category (same code) as they enter the field of observation and you detect opportunities.</td>
</tr>
<tr>
<td>Opportunity:</td>
<td>Defined by one indication at least</td>
</tr>
<tr>
<td>Indication:</td>
<td>Reasons that motivate(s) hand hygiene action, all indications that apply at one moment must be recorded bef.pat: before touching a patient aft.t.: after body fluid exposure risk bef.aept: before clean/aseptic procedure aft.p.: after touching a patient aft.b.f.: after touching patient surroundings</td>
</tr>
</tbody>
</table>
| HH action: | Response to the hand hygiene indication(s); it can be either a positive action by performing handrub or handwash, or a negative action by missing hand hygiene action. HW: hand hygiene action by handwashing with soap and water missed: no hand hygiene action performed.
## Observation Form – Basic Compliance Calculation

### Instructions for use

1. Define the setting outlining the scope for analysis and report related data according to the chosen setting.
2. Check data in the observation form. Hand hygiene actions not related to an indication should not be taken into account and vice versa.
3. Report the session number and the related observation data in the same line. This attribution of session number validates the fact that data has been taken into account for compliance calculation.
4. Results per professional category and per session (vertical):
   4.1 Sum up recorded opportunities (opp) in the case report form per professional category: report the sum in the corresponding cell in the calculation form.
   4.2 Sum up the positive hand hygiene actions related to the total of opportunities above, making difference between handwash (HW) and handrub (HR): report the sum in the corresponding cell in the calculation form.
   4.3 Proceed in the same way for each session (data record form).
   4.4 Add up all sums per each professional category and put the calculation to calculate the compliance rate (given in percent).
5. The addition of results of each line permits to get the global compliance at the end of the last right column.

### Calculation

Compliance (%) = \( \frac{\text{Performend actions}}{\text{Opportunities}} \times 100 \)

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WHO acknowledges the Hôpitaux Universitaires de Genève (HUG), in particular the members of the Infection Control Programme, for their active participation in developing this material.
## Observation Form – Optional Calculation Form

(Indication-related compliance with hand hygiene)

<table>
<thead>
<tr>
<th>Session No.</th>
<th>Before touching a patient</th>
<th>Before a clean/aseptic procedure</th>
<th>After body fluid exposure risk</th>
<th>After touching a patient</th>
<th>After touching patient surroundings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indic (n)</td>
<td>HW (n)</td>
<td>Indic (n)</td>
<td>HW (n)</td>
<td>Indic (n)</td>
</tr>
<tr>
<td></td>
<td>Act (n)</td>
<td></td>
<td>Act (n)</td>
<td></td>
<td>Act (n)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Act (n)</td>
<td></td>
<td>Act (n)</td>
</tr>
</tbody>
</table>

### Instructions for use

1. Define the setting outlining the scope for analysis and report related data according to the chosen setting.
2. Check data in the observation form. Hand hygiene actions not related to an indication should not be taken into account and vice versa.
3. If several indications occur within the same opportunity, each one should be considered separately as well as the related action.
4. Report the session number and the related observation data in the same line. This attribution of session number validates the fact that data has been taken into count for compliance calculation.
   4.1 Sum up indications per indication in the observation form: report the sum in the corresponding cell in the calculation form.
   4.2 Sum up positive hand hygiene actions related to the total of indications above, making the difference between handwash (HW) and handrub (HR): report the sum in the corresponding cell in the calculation form.
   4.3 Proceed in the same way for each session (observation form).
5. Results per indication (indic) and per session (vertical):

*Note: This calculation is not exactly a compliance result, as the denominator of the calculation is an indication instead of an opportunity. Action is artificially overestimated according to each indication. However, the result gives an overall idea of health-care worker’s behaviour towards each type of indication.*
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Patient Safety
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