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Knowing More of the Iceberg: How Detecting a Greater Proportion of Carbapenem-Resistant Enterobacteriaceae Carriers Influences Transmission

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Background. Clinical testing detects a fraction of carbapenem-resistant Enterobacteriaceae (CRE) carriers. Detecting a greater proportion could lead to increased use of infection prevention and control measures but requires resources. Therefore, it is important to understand the impact of detecting increasing proportions of CRE carriers.

Methods. We used our Regional Healthcare Ecosystem Analyst–generated agent-based model of adult inpatient healthcare facilities in Orange County, California, to explore the impact that detecting greater proportions of carriers has on the spread of CRE.

Results. Detecting and placing 1 in 9 carriers on contact precautions increased the prevalence of CRE from 0% to 8.0% county-wide over 10 years. Increasing the proportion of detected carriers from 1 in 9 up to 1 in 5 yielded linear reductions in transmission; at proportions >1 in 5, reductions were greater than linear. Transmission reductions did not occur for 1, 4, or 5 years, varying by facility type. With a contact precautions effectiveness of ≤70%, the detection level yielding nonlinear reductions remained unchanged; with an effectiveness of >80%, detecting only 1 in 5 carriers garnered large reductions in the number of new CRE carriers. Trends held when CRE was already present in the region.

Conclusion. Although detection of all carriers provided the most benefits for preventing new CRE carriers, if this is not feasible, it may be worthwhile to aim for detecting >1 in 5 carriers.

The majority of carbapenem-resistant Enterobacteriaceae (CRE) carriers are unknown because CRE typically is detected by testing done for clinical reasons, such as suspicion of an infection, and because systematic screening is rarely performed outside of active outbreak settings. In other words, only a small fraction of all CRE carriers—the tip of the iceberg—is known (similar to the nosocomial infection iceberg effect described by Weinstein and Kabins [1]). Studies have shown that, on average, the tip of the CRE iceberg may comprise only 1 of every 9 carriers [2–4]; thus, the true CRE burden may be substantially higher than perceived [5]. With CRE's continuing spread [6, 7], the question is whether

more-aggressive testing or surveillance is worthwhile. Knowing a greater proportion of the iceberg (eg, through universal or targeted screening) could lead to better prevention and control measures, The majority of carbapenem-resistant Enterobacteriaceae (CRE) carriers are unknown because CRE typically is detected by testing done for clinical reasons, such as suspicion of an infection, and because systematic screening is rarely performed outside of active outbreak settings. In other words, only a small fraction of all CRE carriers—the tip of the iceberg—is known (similar to the nosocomial infection iceberg effect described by Weinstein and Kabins [1]). Studies have shown that, on average, the tip of the CRE iceberg may comprise only 1 of every 9 carriers [2–4]; thus, the true CRE burden may be substantially higher than perceived [5]. With CRE's continuing spread [6, 7], the question is whether more-aggressive testing or surveillance is worthwhile. Knowing a greater proportion of the iceberg (eg, through universal or targeted screening) could lead to better prevention and control measures, nursing homes) and the patients moving among theses facilities and surrounding communities [11–13, 15–20] to simulate CRE's spread [11, 14]. In this model, each patient was represented by a computational agent. The 2 hallmarks of ABMs are that agents exhibit autonomous decision making and complex adaptive behavior. In our model, each agent took daily actions (eg, getting admitted to a facility, moving to a specific unit, and accepting interventions such as contact precautions) and traveled their own unique paths, independent of other agents (ie, they exhibited autonomous decision making). Also, what occurred to a given agent on one simulated day would then affect what would happen to the agent or what the agent would do on sub-sequent days (eg, if the patient is CRE positive, they will be on contact precautions during the remainder of the hospital stay), which is consistent with complex adaptive behavior.

Briefly, our initial conditions assumed that the region was CRE naive and that, on any given day, a patient can or cannot carry CRE [14]. Each simulated day, patients move from the community or other healthcare facilities into the various OC healthcare facilities. Each facility has a number of beds (matching actual facilities) and multiple units. Patients mix within units in acute care facilities, whereas mixing occurs among all patients in nursing homes to represent their typical high levels of social interaction. Upon admission to a facility, a probability draw determines which unit a patient enters and a second unit– and facility-specific draw determines the patients' length of stay (LOS). A CRE-specific LOS distribution (on average, 7.6 days longer than for noncarriers) determines the estimated LOS for CRE carriers [21]. Using a unit- and facility-specific transmission coefficient (β), patients mix homogenously within assigned units, allowing carriers to transmit CRE to noncarriers daily within each unit (β*susceptible patients*infectious patients). When the LOS elapses, the patient is discharged and can either transfer to another OC facility or enter the community and, after an interval, be or not be readmitted to the same or another facility. Additional details are available in the Supplementary Materials.

CRE carriage was identified via testing (ie, detection of clinical isolates); thus, only a fraction of CRE carriers were known. Only known carriers were placed under con-tact precautions. Contact precautions were retained following transfer to other facilities only if CRE status was communicated (interfacility communication occurred 50% of the time [22]) or if that facility had prior knowledge of the patient's CRE status. Once a facility had knowledge of a patient's CRE status, this knowledge was retained (along with contact precautions) 100% of the time upon readmission to the same facility. Nursing home residents with CRE infection (assumed to be 10% of known carriers) were placed on contact precautions for 10 days because nursing homes usually apply symptom-based contact

precautions. Contact precautions reduced transmission by 40%, which accounted for both efficacy and staff compliance [23–27].

Experiments and Sensitivity Analyses

To evaluate the impact of detecting a greater proportion of the CRE iceberg on transmission and prevalence, we systematically varied the proportion CRE carriers for whom carriage is known (ie, from 1 in 9 carriers to all carriers). This represents the variety of ways of uncovering the iceberg (eg, screening and higher rates of clinical testing). We also systematically varied contact precautions effectiveness (from 40% to 85%; differences represent various adherence levels) and the likelihood of interfacility communication when transferring patients between hospitals (from 50% to 100%). Additional scenarios assumed CRE was already present in the region (starting 10 years after emergence in OC, with a CRE prevalence of 2.6% in acute care hospitals, 28.6% in LTACHs, and 9.5% in nursing homes). We also explored the impact of increasing β coefficients (to twice the parameterized value). Each simulation experiment involved running the model 50 times, with each run consisting of 1000 trajectories for simulation period of 10 years.

RESULTS

Impact of Increasing the Fraction of Detected CRE Carriers on CRE Transmission and Prevalence

Figure 1 shows the impact of increasing the fraction of detected CRE carriers on the CRE prevalence countywide over time since CRE introduction. At the current detection fraction of 1 in 9 carriers, simulation revealed that the CRE prevalence increased from 0% to 8.0% over the 10 simulated years in healthcare facilities countywide, resulting in 11 839 new carriers. Increasing the fraction of detected carriers to 1 in 7 yielded a 2.4% relative reduction in prevalence as compared to detecting 1 in 9 carriers. Further increasing the fraction of detected carriers to 1 in 5, 1 in 3, 1 in 2, and all carriers resulted in a 4.6%, 6.6%, 17.5%, and 70.5% relative decrease in prevalence at year 10, respectively, compared with detecting 1 in 9 carriers.

Table 1 shows the total number of prevented cases of carriage at different time points by facility type when increasing the pro-portion of detected CRE carriers. The sum of corresponding cells for each facility type in Table 1 gives the total number of prevented cases in healthcare facilities countywide. For ex-ample, when detecting 1 in 3 carriers as carriers compared to 1 in 5 carriers, 1661 new cases of carriage would be prevented countywide (13 in acute care hospitals, 978 in LTACHs, and 670 in nursing homes) over 10 years. Increasing the fraction of CRE carriers detected resulted in nonlinear trends in the marginal number of new prevented; these nonlinear gains started to appear when detecting at least 1 in 5 carriers. These trends held with higher β coefficients; while the total number of CRE carriers increased, nonlinear gains continued to appear when detecting at least 1 in 5 carriers.

For the same detection level, the relative reduction of CRE prevalence was lower when CRE was already present as compared to the prevalence after CRE emerged (Figure 2). For example, increasing the fraction detected resulted in a ≤30.0% relative reduction in CRE prevalence countywide as compared to detecting 1 in 9 carriers. However, the overall trends were similar, and increasing the fraction of carriers detected resulted in nonlinear trends in the marginal number of new carriage cases prevented, which start to appear when detecting at least 1 in 5 carriers (Table 2).

Impact of Increasing the Fraction of Detected CRE Carriers Across Facilities Types

At the current fraction of 1 in 9 CRE carriers detected, prevalence increased from 0% to 2.6% in acute care hospitals, to 28.6% in LTACHs, and to 9.5% in nursing homes over 10 years (Figure 1B–D). The magnitude of the relative reduction (4%–70%) in CRE prevalence when increasing the fraction of CRE carriers detected was similar across all facility types, with substantial gains accrued when detecting >1 in every 5 carriers as increases in benefits become nonlinear. While relative reductions in prevalence and detection thresholds were sim-ilar, the number of prevented cases differed substantially by facility type (Table 1). Over 10 simulated years, OC hospitals had 74.2 CRE hospital transmission events, with 23 averted by detecting 1 in 3 carriers (Table 1). However, hospitals detected 687.1 "new" CRE carriers (ie, cases previously unknown when detecting 1 in 9 carriers) over 10 years, of which up to 612.8 represent transmissions that occurred elsewhere. Table 1 also shows the benefits of increasing detection from other starting levels (eg, increasing detection from 1 in 7 to 1 in 3 CRE carriers for 6 years prevented 767.5 new cases of carriage in LTACHs). Again, results were robust to increases in β coefficients.

Overall, the countywide reduction in CRE carriage was largely driven by prevention of cases garnered in LTACHs (Table 1 and Figure 1). Differences across all facility types were disproportionate in magnitude not only by facility type, but also on a per facility basis. For example, when all facilities detected 1 in 5 carriers as compared to 1 in 9 carriers, the median number of new carriers decreased by 143.6 (range, 28.8–238.3) in a single LTACH, by 0.3 (range, 0.03–1.7) in a single hospital, and by 5.4 (range, 0–16.7) in a single nursing home over 10 years (data not shown).

When CRE was already present, relative reductions in CRE prevalence when increasing the fraction of CRE carriers detected differed by facility type (eg, 19%, 32%, and 11% in acute care hospitals, LTACHs, and nursing homes, respectively, when detecting 1 in 2 carriers as compared to 1 in 9 carriers). However, across all facility types, substantial reductions in CRE prevalence and in the marginal number of new carriers prevented (Table 2) appeared when detecting >1 in 5 carriers, as increases in benefits become nonlinear. Similarly, countywide reductions in CRE prevalence and transmission were driven by the reductions in LTACHs (Figure 2 and Table 2).

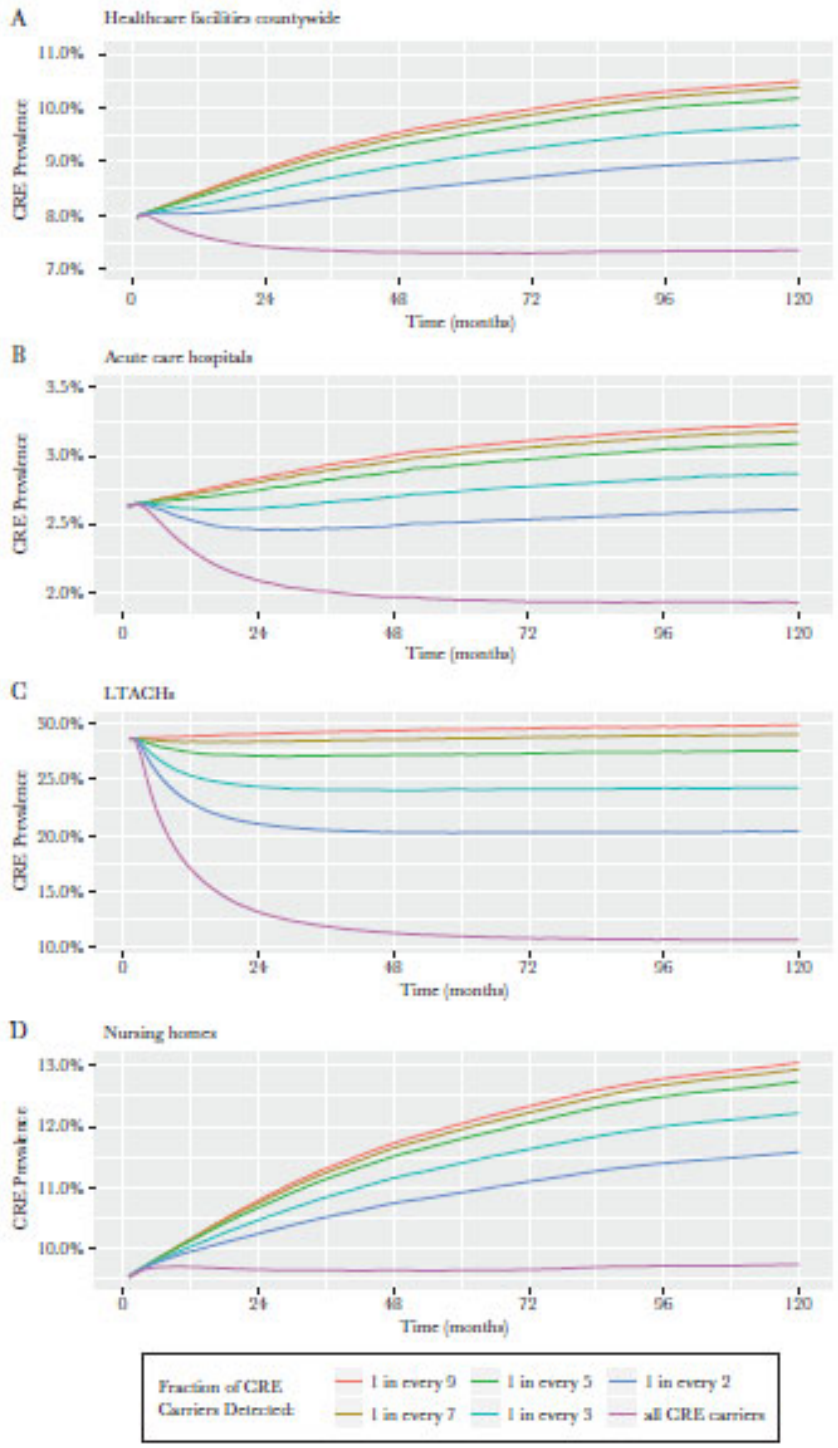

Figure 2. Simulated average prevalence of carbapenem-resistant Enterobacteriaceae (CRE) over time when detecting various fractions of CRE carriers in all healthcare facilities when CRE is already present in all healthcare facilities countywide (A), acute care hospitals countywide (B), long-term acute care hospitals (LTACHs) countywide (C), and nursing homes countywide (D). Scenarios assumed a 40% effectiveness of contact precautions and a 50% likelihood of interfacility communication of a transferring patient's CRE status.

Table 2. New Carbapenem-Resistant Enterobacteriaceae (CRE) Carriers Prevented in Orange County, California (OC), Healthcare Facilities When CRE Was Already Present, at Different Points in Time When Increasing the Proportion of Detected CRE Carriers in All OC Healthcare Facilities

	New Carriers Prevented, Cumulative No.				
	Year 2	Year 4	Year 6	Year 8	Year 10
Acute Care Hospitals (N=23)					
From detecting 1 in 9 carriers to detecting 1 in 7 carriers	0.44	1.14	2.07	3.01	3.93
From detecting 1 in 9 carriers to detecting 1 in 5 carriers	1.28	3.37	5.74	8.22	10.76
From detecting 1 in 9 carriers to detecting 1 in 3 carriers	3.26	8.23	13.87	19.76	25.81
From detecting 1 in 9 carriers to detecting 1 in 2 carriers	5.47	13.70	22.94	32.58	42.55
From detecting 1 in 9 carriers to detecting all carriers	10.46	25.42	42.10	59.71	77.91
From detecting 1 in 7 carriers to detecting 1 in 5 carriers	0.84	2.23	3.66	5.21	6.83
From detecting 1 in 7 carriers to detecting 1 in 3 carriers	2.82	7.09	11.80	16.75	21.88
From detecting 1 in 7 carriers to detecting 1 in 2 carriers	5.03	12.56	20.86	29.57	38.62
From detecting 1 in 7 carriers to detecting all carriers	10.02	24.28	40.02	56.70	73.98
From detecting 1 in 5 carriers to detecting 1 in 3 carriers	1.98	4.86	8.13	11.54	15.05
From detecting 1 in 5 carriers to detecting 1 in 2 carriers	4.19	10.33	17.20	24.36	31.79
From detecting 1 in 5 carriers to detecting all carriers	9.18	22.05	36.36	51.49	67.15
From detecting 1 in 3 carriers to detecting 1 in 2 carriers	2.21	5.47	9.07	12.82	16.74
From detecting 1 in 3 carriers to detecting all carriers	7.20	17.19	28.23	39.95	52.10
From detecting 1 in 2 carriers to detecting all carriers	4.99	11.72	19.16	27.13	35.36
Long-Term Acute Care Hospitals (LTACHs, N=5)					
From detecting 1 in 9 carriers to detecting 1 in 7 carriers	33.6	83.6	137.1	190.1	243.4
From detecting 1 in 9 carriers to detecting 1 in 5 carriers	97.1	236.9	383.2	529.4	676.9
From detecting 1 in 9 carriers to detecting 1 in 3 carriers	234.9	571.0	920.2	1,274.6	1,631.4
From detecting 1 in 9 carriers to detecting 1 in 2 carriers	393.5	956.6	1,541.7	2,134.5	2,729.6
From detecting 1 in 9 carriers to detecting all carriers	764.2	1,839.1	2,964.3	4,107.4	5,258.2
From detecting 1 in 7 carriers to detecting 1 in 5 carriers	63.5	153.3	246.0	339.3	433.6
From detecting 1 in 7 carriers to detecting 1 in 3 carriers	201.2	487.4	783.1	1,084.5	1,388.1
From detecting 1 in 7 carriers to detecting 1 in 2 carriers	359.9	873.0	1,404.6	1,944.4	2,486.3
From detecting 1 in 7 carriers to detecting all carriers	730.5	1,755.4	2,827.2	3,917.2	5,014.9
From detecting 1 in 5 carriers to detecting 1 in 3 carriers	137.7	334.1	537.1	745.2	954.5
From detecting 1 in 5 carriers to detecting 1 in 2 carriers	296.4	719.7	1,158.5	1,605.1	2,052.7
From detecting 1 in 5 carriers to detecting all carriers	667.1	1,602.2	2,581.2	3,578.0	4,581.3
From detecting 1 in 3 carriers to detecting 1 in 2 carriers	158.6	385.6	621.4	859.9	1,098.2
From detecting 1 in 3 carriers to detecting all carriers	529.3	1,268.1	2,044.1	2,832.7	3,626.8
From detecting 1 in 2 carriers to detecting all carriers	370.7	882.5	1,422.6	1,972.8	2,528.6
Nursing Homes (N=74)					
From detecting 1 in 9 carriers to detecting 1 in 7 carriers	2.2	15.4	34.0	53.9	73.9
From detecting 1 in 9 carriers to detecting 1 in 5 carriers	8.1	42.6	91.2	144.0	201.1
From detecting 1 in 9 carriers to detecting 1 in 3 carriers	29.1	122.1	248.0	392.6	545.3
From detecting 1 in 9 carriers to detecting 1 in 2 carriers	48.8	207.6	428.6	683.6	956.1
From detecting 1 in 9 carriers to detecting all carriers	106.5	443.1	923.3	1,494.2	2,118.3
From detecting 1 in 7 carriers to detecting 1 in 5 carriers	5.9	27.2	57.2	90.1	127.2
From detecting 1 in 7 carriers to detecting 1 in 3 carriers	26.9	106.7	214.0	338.7	471.4
From detecting 1 in 7 carriers to detecting 1 in 2 carriers	46.6	192.2	394.6	629.7	882.2
From detecting 1 in 7 carriers to detecting all carriers	104.3	427.7	889.3	1,440.3	2,044.5
From detecting 1 in 5 carriers to detecting 1 in 3 carriers	21.0	79.5	156.8	248.6	344.2
From detecting 1 in 5 carriers to detecting 1 in 2 carriers	40.7	165.0	337.5	539.7	755.1
From detecting 1 in 5 carriers to detecting all carriers	98.4	400.5	832.1	1,350.2	1,917.3
From detecting 1 in 3 carriers to detecting 1 in 2 carriers	19.7	85.5	180.7	291.0	410.8
From detecting 1 in 3 carriers to detecting all carriers	77.4	321.0	675.3	1,101.5	1,573.0
From detecting 1 in 2 carriers to detecting all carriers	57.7	235.5	494.7	810.5	1,162.2

Impact of Increasing the Fraction of Detected CRE Carriers Over Time

The benefits of detecting more CRE carriers could take years to accrue but varied by facility type (Table 1 and Figure 1). In both acute care hospitals and nursing homes, small differences in CRE prevalence began to manifest after a year for higher detection levels, while LTACHs started to see small differences after approximately 6 months. However, for lower detection levels (eg, 1 in 9 and 1 in 7 carriers), differences took longer to manifest (Figure 1). Nevertheless, in all facilities, the greatest prevention of transmission did not occur for several years. Additionally, the marginal benefits grew over time. For example, in acute care hospitals, increasing the fraction of detected CRE carriers from 1 in 7 to 1 in 5 prevented a similar number of transmission events as did increasing the fraction from 1 in 9 to 1 in 7 during years 1–5; however, by year 5, larger marginal gains started to manifest, and detecting 1 in 5 carriers prevented a larger number of transmission events. In LTACHs and nursing homes, larger marginal benefits were seen by year 1 and year 4, respectively (Table 1).

The benefits of detecting more CRE carriers appeared faster and tended to stabilize after a few years when CRE was already present (Figure 2 and Table 2). Differences began to manifest within 6 months for higher detection levels but could take >2 years for lower detection levels in hospitals and nursing homes.

Impact of Varying Contact Precautions Effectiveness

Figure 3 shows how the number of new CRE carriers varied over time when increasing the fraction of detected CRE carriers at different levels of contact precautions effectiveness (ie, representing various adherence levels). The splay between the lines decreases as contact precautions effectiveness increase; thus, at higher effectiveness levels, the marginal gains become more linear. With ≤70% contact precautions effectiveness, increases in the fraction of detected carriers were generally not enough to garner large reductions in CRE transmission unless > 1 in 5 carriers were detected, at which point gains became nonlinear. For example, with 50% contact precautions effective-ness, larger gains were not garnered until 1 in 3 carriers were detected (Figure 3). However, with ≥80% contact precautions effectiveness, large reductions in CRE cases were seen when only detecting 1 in 5 carriers, and increasing detection resulted in linear reductions.

In some cases, there were fewer CRE transmission events with a higher contact precautions effectiveness and smaller fraction of carriers detected than with a lower effectiveness and higher fraction detected (eg, detecting 1 in every 9 carriers with 80% contact precautions effectiveness resulted in fewer transmission events over time than detecting 1 in every 5 carriers with 60% contact precautions effectiveness). Thus, when detecting a lower fraction of carriers, increases in contact precautions effective-ness may have a larger impact than detecting more carriers on the number of new CRE carriers. Figure 3 also highlights how these differences between detection levels were magnified over time and how the trends differed among the facility types.

Similar trends were seen with a higher CRE prevalence. Again, increasing the fraction of detected carriers with ≤70% contact precautions effectiveness resulted in nonlinear marginal differences when detecting at least 1 in 5 carriers, and with ≥80% contact precautions effectiveness, detecting only 1 in 5 carriers resulted in large reductions in new carriers. The relative decrease in CRE prevalence

increased for the different detection levels with increases in contact precautions effectiveness (Figure 4).

CRE prevalence, respectively, when detecting all as compared to 1 in 9 carriers. At higher levels of contact precautions effective-ness, the marginal gains became more linear.

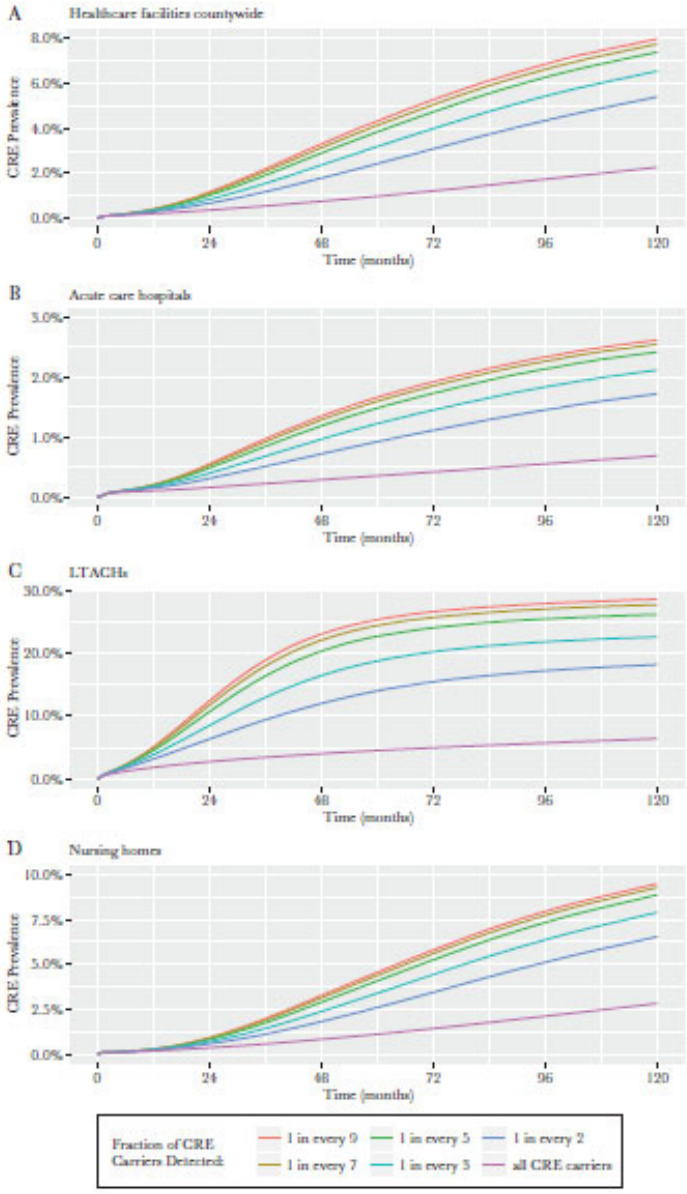

Figure 1. Simulated average prevalence of carbapenem-resistant Enterobacteriaceae (CRE) over time when detecting various fractions of CRE carriers in all healthcare facilities since CRE introduction in all healthcare facilities countywide (A), acute care hospitals countywide (B), long-term acute care hospitals (LTACHs) countywide (C), and nursing homes countywide (D). Scenarios assumed a 40% effectiveness of contact precautions and a 50% likelihood of interfacility communication of a transferring patient's CRE status.

Table 1. New Carbapenem-Resistant Enterobacteriaceae (CRE) Carriers Prevented in Orange County, California (OC), Healthcare Facilities After CRE Introduction, at Different Points in Time when Increasing the Proportion of Detected CRE Carriers in All OC Healthcare Facilities

	New Carriers Prevented, Cumulative No.				
	Year 2	Year 4	Year 6	Year 8	Year 10
Acute Care Hospitals (N=23)					
From detecting 1 in 9 carriers to detecting 1 in 7 carriers	0.14	0.73	1.60	2.51	3.49
From detecting 1 in 9 carriers to detecting 1 in 5 carriers	0.33	1.86	4.19	6.82	9.60
From detecting 1 in 9 carriers to detecting 1 in 3 carriers	0.73	4.22	9.68	15.97	22.67
From detecting 1 in 9 carriers to detecting 1 in 2 carriers	1.11	6.46	15.20	25.59	36.76
From detecting 1 in 9 carriers to detecting all carriers	1.74	9.85	23.86	41.71	61.94
From detecting 1 in 7 carriers to detecting 1 in 5 carriers	0.19	1.13	2.59	4.31	6.11
From detecting 1 in 7 carriers to detecting 1 in 3 carriers	0.60	3.49	8.07	13.46	19.18
From detecting 1 in 7 carriers to detecting 1 in 2 carriers	0.97	5.72	13.60	23.08	33.28
From detecting 1 in 7 carriers to detecting all carriers	1.60	9.11	22.26	39.19	58.45
From detecting 1 in 5 carriers to detecting 1 in 3 carriers	0.40	2.36	5.49	9.14	13.07
From detecting 1 in 5 carriers to detecting 1 in 2 carriers	0.78	4.59	11.01	18.77	27.16
From detecting 1 in 5 carriers to detecting all carriers	1.41	7.98	19.67	34.88	52.34
From detecting 1 in 3 carriers to detecting 1 in 2 carriers	0.37	2.23	5.52	9.62	14.09
From detecting 1 in 3 carriers to detecting all carriers	1.01	5.62	14.18	25.74	39.27
From detecting 1 in 2 carriers to detecting all carriers	0.63	3.39	8.66	16.12	25.18
Long-Term Acute Care Hospitals (LTACHs, N=5)					
From detecting 1 in 9 carriers to detecting 1 in 7 carriers	21.1	80.4	140.6	197.4	252.9
From detecting 1 in 9 carriers to detecting 1 in 5 carriers	54.7	215.0	383.6	542.6	696.6
From detecting 1 in 9 carriers to detecting 1 in 3 carriers	122.5	498.1	908.1	1,296.8	1,676.0
From detecting 1 in 9 carriers to detecting 1 in 2 carriers	190.2	792.0	1,487.7	2,156.0	2,802.7
From detecting 1 in 9 carriers to detecting all carriers	309.0	1,288.3	2,545.1	3,854.4	5,165.7
From detecting 1 in 7 carriers to detecting 1 in 5 carriers	33.7	134.6	243.0	345.2	445.7
From detecting 1 in 7 carriers to detecting 1 in 3 carriers	101.5	417.8	767.5	1,099.3	1,423.1
From detecting 1 in 7 carriers to detecting 1 in 2 carriers	169.1	711.7	1,347.1	1,958.6	2,549.9
From detecting 1 in 7 carriers to detecting all carriers	287.9	1,207.9	2,404.5	3,657.0	4,912.8
From detecting 1 in 5 carriers to detecting 1 in 3 carriers	67.8	283.1	524.5	754.2	977.5
From detecting 1 in 5 carriers to detecting 1 in 2 carriers	135.4	577.0	1,104.1	1,613.4	2,104.2
From detecting 1 in 5 carriers to detecting all carriers	254.3	1,073.3	2,161.4	3,311.9	4,467.1
From detecting 1 in 3 carriers to detecting 1 in 2 carriers	67.6	293.9	579.6	859.2	1,126.7
From detecting 1 in 3 carriers to detecting all carriers	186.5	790.1	1,636.9	2,557.7	3,489.7
From detecting 1 in 2 carriers to detecting all carriers	118.9	496.3	1,057.3	1,698.4	2,363.0
Nursing Homes (N=74)					
From detecting 1 in 9 carriers to detecting 1 in 7 carriers	2.8	25.0	64.6	109.3	153.7
From detecting 1 in 9 carriers to detecting 1 in 5 carriers	7.7	67.3	179.1	310.8	442.8
From detecting 1 in 9 carriers to detecting 1 in 3 carriers	17.2	157.6	432.7	769.4	1,112.8
From detecting 1 in 9 carriers to detecting 1 in 2 carriers	27.6	252.4	718.8	1,319.9	1,955.4
From detecting 1 in 9 carriers to detecting all carriers	46.7	418.5	1,257.7	2,470.7	3,900.9
From detecting 1 in 7 carriers to detecting 1 in 5 carriers	4.8	42.3	114.4	201.5	289.2
From detecting 1 in 7 carriers to detecting 1 in 3 carriers	14.4	132.6	368.1	660.1	959.1
From detecting 1 in 7 carriers to detecting 1 in 2 carriers	24.8	227.4	654.2	1,210.7	1,801.7
From detecting 1 in 7 carriers to detecting all carriers	43.9	393.5	1,193.1	2,361.5	3,747.3
From detecting 1 in 5 carriers to detecting 1 in 3 carriers	9.6	90.2	253.6	458.6	669.9
From detecting 1 in 5 carriers to detecting 1 in 2 carriers	19.9	185.1	539.8	1,009.1	1,512.6
From detecting 1 in 5 carriers to detecting all carriers	39.0	351.1	1,078.6	2,159.9	3,458.1
From detecting 1 in 3 carriers to detecting 1 in 2 carriers	10.4	94.8	286.1	550.5	842.6
From detecting 1 in 3 carriers to detecting all carriers	29.5	260.9	825.0	1,701.3	2,788.2
From detecting 1 in 2 carriers to detecting all carriers	19.1	166.1	538.9	1,150.8	1,945.5

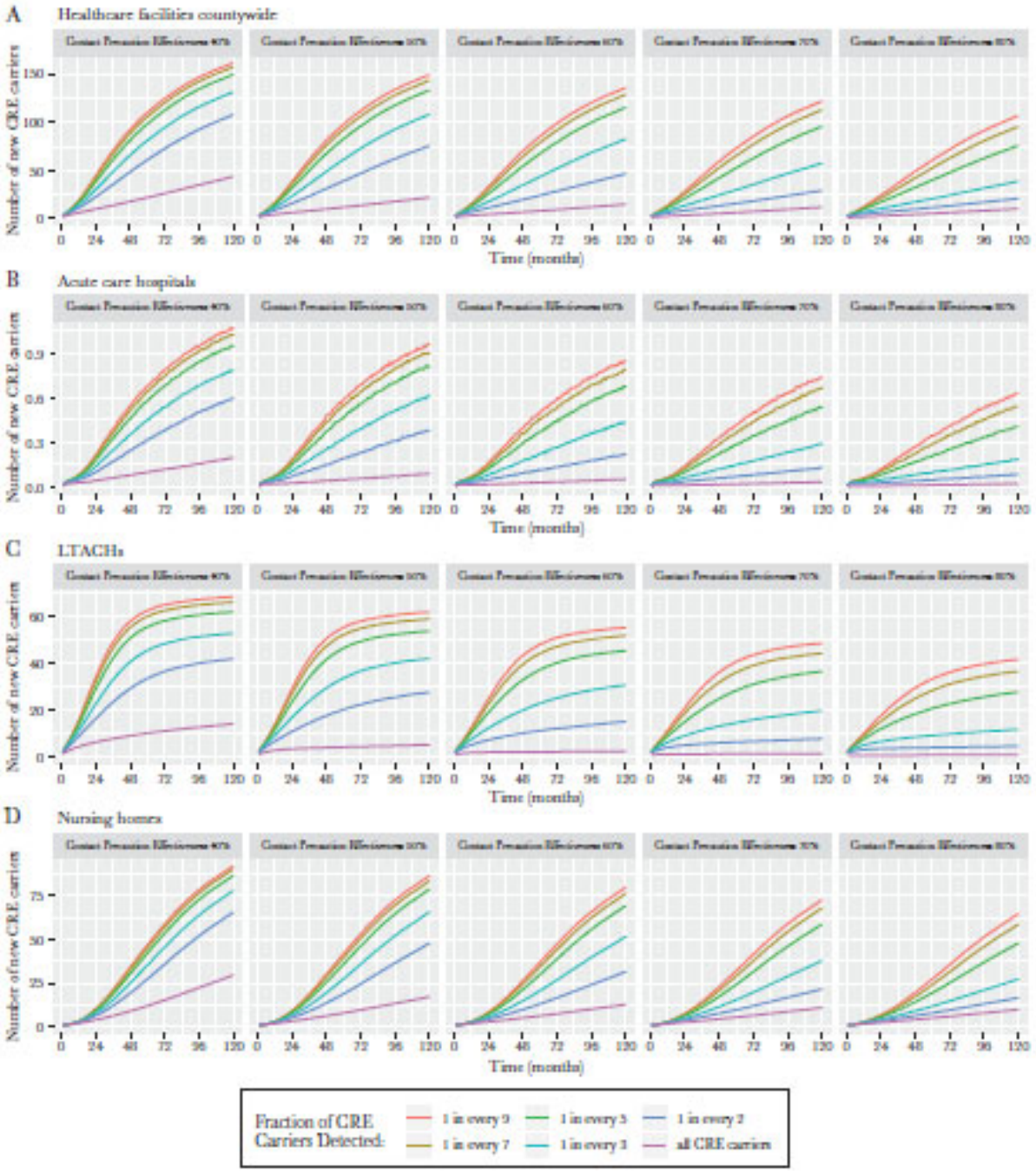

Figure 3. Number of new carbapenem-resistant Enterobacteriaceae (CRE) carriers per month since CRE introduction over 10 years when increasing the fraction of CRE carriers detected in all healthcare facilities countywide and by facility type for various levels of contact precautions effectiveness. Scenarios assumed 50% likelihood of interfacility communication of a transferring patient's CRE status.

Impact of Varying Interfacility Communication

Regardless of CRE's starting prevalence, results were robust to changes in interfacility communication. Even with perfect communication about CRE status between transferring facilities, marginal reductions in new CRE carriers became greater than linear when detecting more than 1 in 5 carriers.

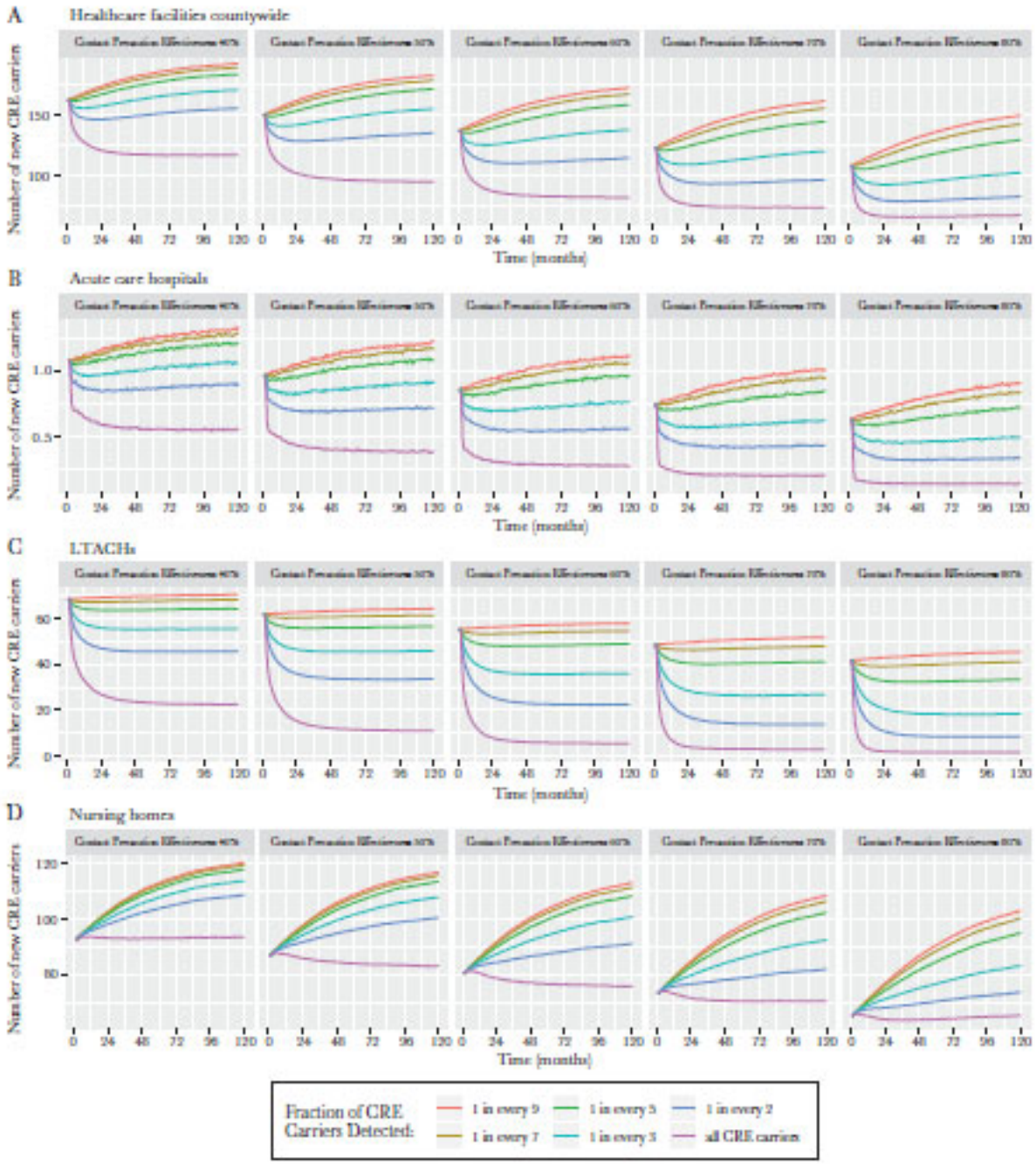

Figure 4. Number of new carbapenem-resistant Enterobacteriaceae (CRE) carriers per month when CRE was already present over 10 years when increasing the fraction of CRE carriers detected in all healthcare facilities countywide and by facility type for various levels of contact precautions effectiveness. Scenarios assumed 50% likelihood of interfacility communication of a transferring patient's CRE status.

DISCUSSION

Our results show that, although knowing all CRE carriers would provide the greatest reduction in CRE transmission, if this is not feasible then it may be worthwhile to aim for detecting >1 in every 5 carriers in regions where CRE is emerging or has a high prevalence. Substantial nonlinear gains occur when >1 in 5 CRE carriers are detected (ie, at least 1 in 4 carriers). This threshold represents a tipping point whereby a sufficient number of the patients comprising the underlying CRE burden is known and placed under contact precautions to substantially dampen transmission. Detecting ≤1 in 5 carriers still leaves a significant number of CRE carriers unknown, and isolation of known carriers is not enough to meaningfully interrupt transmission. These findings generally hold despite varying CRE starting prevalence, contact precautions effectiveness, and interfacility communication. Ranging contact precautions effectiveness between 40% and 70% did not affect the conclusion of the threshold; however, at 80% effectiveness, substantial reductions in CRE were noted when detecting 1 in 5 carriers. On the other hand, communication of CRE status between transferring facilities had very little effect on the benefits of increasing the fraction of CRE carriers detected.

Our results also show that the countywide effect of increased detection does not fully manifest until year 4 (or year 2, with higher starting prevalence) unless a high fraction of carriers is detected. In general, a year is not enough time to see an impact on CRE spread, because benefits accrue over years. In fact, in acute care hospitals, sizeable gains were not noted until year 5, and nursing homes gains were not achieved until year 4 (years 4 and 2, respectively, with a higher prevalence). On the other hand, LTACHs see meaningful gains after a year (or after 6 months, with a higher prevalence). This highlights the need to measure the value of intervention programs after several years, since gains may not be immediate and effective interventions may be falsely deemed unsuccessful. Increased detection yields a faster return of benefits, as gains accrue faster when more CRE carriers are known (eg, detecting at least 1 in every 3 carriers).

Another key finding is that LTACHs are the highest-yield locations for interventions that increase CRE detection to decrease transmission. LTACHs have a greater CRE prevalence than other facilities [28–30]; they have a higher admission prevalence, longer patient LOS, smaller bed capacity, and substantial interconnectivity with other facilities—all of which facilitate a higher CRE prevalence. Given this, the reductions seen by detecting and isolating larger proportions of the underlying burden can be substantial. Thus, if resources are limited, LTACHs may be an efficient target for screening efforts to increase CRE detection. Additionally, countywide effects were largely driven by reductions gained in LTACHs, followed by those in nursing homes. Importantly, if nursing homes implemented contact precautions in >10% of known CRE cases (as was done in our scenarios), the gains could be substantially larger. While acute care hospitals had the fewest number of actual CRE transmissions, routine culturing practices lead hospitals to identify a large number of previously unknown carriers, even when detecting 1 in 9 carriers. Depending on the day the culture is done, these cases may appear to be attributed to the hospitals, regardless of where CRE was actually acquired.

The critical detection threshold did not change when increasing the chances that a facility transferring a patient with CRE would inform the receiving facility of the patient's status. This does not mean that there is no benefit of such communication. Rather, it shows that the detection threshold is really driven by more than just the direct transfers. For example, as our previous work has demonstrated, a large percentage of patient sharing is indirect (eg, patients move from one facility to the community and then later get readmitted to another facility) [9, 10]. Focusing just on direct transfers would capture only a small percentage of patients with CRE who would need to be on contact precautions.

Our results demonstrate the need for more-aggressive detection of CRE carriers who do not have clinically apparent infections. Previous studies have shown that the percentage of carriers who develop clinically apparent infections can be as low as 5% (and as high as 45%) [31, 32]. If 1 in 5 carriers is the critical detection threshold, waiting until CRE manifests clinically could result in a gap of 15%. There are many ways to identify more CRE carriers, including active surveillance (eg, screening on admission or periodically during an inpatient stay), changing the standards of care to increase testing rates, and improving the sharing of patient information between facilities. While knowing 100% of CRE carriers (ie, perfect knowledge) is un-likely without perfect testing and universal surveillance, there are different levels of surveillance that can increase and further elucidate CRE's underlying burden. For example, surveillance can be performed at different levels of care (eg, in intensive care units), on admission, hospital wide, or in different facility types (eg, only in LTACHs). However, all of these take time, effort, and resources. Thus, it is important to understand the benefits of detecting and isolating more carriers and the extent to which the CRE burden should be uncovered in specific facilities at different points of the CRE epidemic. Our results suggest that the trade-off in resource use would be much better when >1 in 5 carriers are detected, especially in LTACHs.

Our study showed that the key detection threshold (knowing >1 in 5 carriers) was robust to changes in CRE prevalence, contact precautions effectiveness, and interfacility communication. As demonstrated by our previous publications, OC has a heterogeneous set of health-care facilities and patient sharing patterns [9, 10], meaning that our sensitivity analyses that altered different parameters could capture a fairly wide range of circumstances. This suggests that our findings could apply to other regions. Of course, the question remains whether our findings would apply to all other regions, including those that have very different composition of facilities (eg, significantly more LTACHs). Since our RHEA platform can be used to generate ABMs of any region and its healthcare facilities [16, 33], future work can involve developing models of other regions and determining more definitively how our findings may hold or change across a broader range of circumstances.

Our study had some limitations. All models are simplifications of real life and cannot represent all situations and outcomes. Our results assumed that the proportion of known CRE carriers was constant over the simulated period, but in reality this would likely vary in different facilities or over time. We did not ac-count for the possibility that certain patients spread CRE at higher rates (eg, ventilator dependency). Our model did not include pediatric transmission, although literature suggests that children are not commonly CRE carriers and thus not major drivers of transmission.

In summary, while knowing all carriers certainly would pro-vide the most benefits, if this not feasible then it may be worth-while to aim for detecting >1 in 5 carriers. Detecting 1 in 5 carriers

provided benefits particularly in conjunction with an ≥80% effectiveness of contact precautions. Effects of increased detection take at least 1 and potentially many years to manifest and accrue over time.

SUPPLEMENTARY DATA

Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The funders did not in any way restrict our ability or right to publish any analyses, results, or interpretations of results that emerged from this study. Companies contributing products to Orange County hospitals and nursing homes had no role in the design or conduct of the study, the analysis of data, or the publication of findings.

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Potential conflicts of interest. L. G. M., J. A. M., and S. S. H. are conducting other clinical studies in which Orange County hospitals and nursing homes receive contributed products from Sage Products, 3M, Xttrium, Clorox, and Medline. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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