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Referrals, access, and equity of monoclonal antibodies for outpatient COVID-19

A qualitative study of clinician perspectives

Mika K. Hamer, PhD, MPH[a,b,*], Ahmed Alasmar, BS[b], Bethany M. Kwan, PhD, MSPH[c,d,e], Matthew K. Wynia, MD, MPH[b,e,f], Adit A. Ginde, MD, MPH[c,e], Matthew W. DeCamp, MD, PhD[b,e,f]

Abstract

Neutralizing monoclonal antibody treatments for non-hospitalized patients with COVID-19 have been available since November 2020. However, they have been underutilized and access has been inequitable. To understand, from the clinician perspective, the factors facilitating or hindering monoclonal antibody referrals, patient access, and equity to inform development of clinician-focused messages, materials, and processes for improving access to therapeutics for COVID-19 in Colorado. We interviewed 38 frontline clinicians with experience caring for patients with COVID-19 in outpatient settings. Clinicians were purposely sampled for diversity to understand perspectives across geography (i.e., urban versus rural), practice setting, specialty, and self-reported knowledge about monoclonal antibodies. Interviews were conducted between June and September 2021, lasted 21 to 62 minutes, and were audio recorded and transcribed verbatim. Interview transcripts were then analyzed using rapid qualitative analysis to identify thematic content and to compare themes across practice settings and other variables. Clinicians perceived monoclonal antibodies to be highly effective and were unconcerned about their emergency use status; hence, these factors were not perceived to hinder patient referrals. However, some barriers to access – including complex and changing logistics for referring, as well as the time and facilities needed for an infusion – inhibited widespread use. Clinicians in small, independent, and rural practices experienced unique challenges, such as lack of awareness of their patients' COVID-19 test results, disconnect from treatment distribution systems, and patients who faced long travel times to obtain treatment. Many clinicians held a persistent belief that monoclonal antibodies were in short supply; this belief hindered referrals, even when monoclonal antibody doses were not scarce. Across practice settings, the most important facilitator for access to monoclonal antibodies was linkage of COVID-19 testing and treatment within care delivery. Although clinicians viewed monoclonal antibodies as safe and effective treatments for COVID-19, individual- and system-level barriers inhibited referrals, particular in some practice settings. Subcutaneous or oral formulations may overcome certain barriers to access, but simplifying patient access by linking testing with delivery of treatments that reduce morbidity and mortality will be critical for the ongoing response to COVID-19 and in future pandemics.

Abbreviations: CDPHE = Colorado Department of Public Health and Environment, DOI = diffusion of innovations, FDA = Food and Drug Administration, mAb = monoclonal antibody.

Keywords: acute care, COVID-19, diffusion of innovation, dissemination and implementation, primary care

1. Introduction

The earliest days of the COVID-19 pandemic were characterized by uncertainty and few options for treating patients not ill enough to be hospitalized.[1] In November 2020, when the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for bamlanivimab, the first neutralizing monoclonal antibody (mAb) treatment for use in outpatient settings for patients at high risk of progressing to severe disease, states and the federal government assumed demand would far outstrip supply.[2] Additional mAbs were authorized throughout spring and summer 2021;[3–5] subsequent clinical trials and real world data have demonstrated that mAbs reduced hospitalizations for high-risk outpatients with COVID-19 by as much as 70-80%.[6–11] Yet use of these therapies has been far less than expected.

Anticipating surging demand and limited supplies in late 2020 and early 2021, the federal government tasked state health departments with allocating mAbs and some, including in Colorado,

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[a] Department of Health Systems, Management, and Policy, Colorado School of Public Health, Aurora, CO, [b] Center for Bioethics and Humanities, University of Colorado Anschutz Medical Campus, Aurora, CO, [c] Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, [d] Department of Family Medicine, University of Colorado School of Medicine, Aurora, CO, [e] Colorado Clinical & Translational Sciences Institute, University of Colorado Anschutz Medical Campus, Aurora, CO, [f] Division of General Internal Medicine, University of Colorado School of Medicine, Aurora, CO.

** Correspondence: Mika K. Hamer, Center for Bioethics and Humanities, University of Colorado Anschutz Medical Campus, 13080 E. 19th Ave, Mail Stop B137, Aurora CO 80045 (e-mail: mika.hamer@cuanschutz.edu).*

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launched state-wide systems to facilitate equitable access. Yet by March 2021, only 5% of Colorado's allocated doses had been used.[12] Similar lack of uptake was occurring across the country, and leaders of the federal COVID-19 response were unable to explain why demand was not outpacing supply.[13] At the same time, disparities in access to mAbs among Hispanic, Black, Asian, and other nonwhite communities were noted, raising concerns that barriers to referral and access to mAbs were not being experienced equitably across all communities.[14]

Several reasons have been proposed for the slow adoption of mAbs. Patients and clinicians may be wary of costs, not realizing these therapies were paid for by the federal government (though some patients might have to pay for the cost of infusion). For busy clinicians, remaining current on rapidly changing evidence and referral processes could be challenging. For example, the FDA expanded mAb eligibility criteria in Summer 2021, greatly increasing the proportion of the US population eligible.[15] Authorization of a mAb that could be delivered by subcutaneous injection in June 2021 expanded access outside of infusion settings. Early in 2021, mAb doses were allocated to states by the federal government and states managed distribution, but from March to September treatment sites could direct-order from the federal supplier, followed by a return to state/territory allocation in mid-September.

To date however, there is little information about what clinicians perceive to be barriers to uptake of mAbs. We conducted a qualitative study to understand the factors facilitating or hindering mAb referrals (i.e., the ability of the clinician to navigate the process of referring a patient for mAbs), access (i.e., whether a patient can actually receive mAbs, based on a referral), and equity (i.e., whether all patients have fair access to mAbs) to inform development of clinician-focused messages, materials, and processes for improving access to novel COVID-19 therapeutics in Colorado and other states.

2. Methods

2.1. Study design

This qualitative study was one part of a large, multi-method NIH-funded project to support rapid, equitable access to mAbs in Colorado, which had the overarching goals of identifying factors related to community and clinician awareness of mAb referral processes and evaluating real-world effectiveness of mAbs for high-risk outpatients with COVID-19.[16] Results from additional components of the study, including a state-wide clinician survey[17] and community member surveys and focus groups,[18] are reported elsewhere. In this study, we used qualitative interviews, guided by the diffusion of innovation (DOI) theory[19] to identify factors that served as facilitators or barriers to clinicians' use of mAb referrals and treatment. Findings from the multiple components of the larger investigation were used to inform implementation of efforts, such as clinician-focused education, to increase equitable access to mAbs statewide.

2.2. Sample

We interviewed Colorado-based physicians and advanced practice providers who care for outpatients with COVID-19. We aimed to recruit approximately 36 interview participants[20] who were identified from a state-wide clinician survey about mAb use in Colorado.[17] We purposefully sampled for diversity to understand perspectives across geography (i.e., urban versus rural), practice setting (i.e., community-based clinics, hospital-based outpatient clinics, long-term care facilities, Federally Qualified Health Centers, and emergency departments), clinician specialty, and self-reported mAb knowledge.

2.3. Interview protocol and procedures

To achieve the study objectives, we designed a semi-structured interview guide based on DOI domains (interview guide available upon request).[21] It explored several DOI domains, including perceived attributes of the innovation (such as evidence for efficacy and safety); systems of communication and influence about mAbs; characteristics of the implementation process used for mAb referral and treatment; and characteristics of the practice setting that support or hinder adoption (i.e., the inner context). Within each of these domains we expected to identify facilitating and hindering factors related to to mAb referral, patient access, and equitable distribution.

Two members of the team (MH and MD) conducted phone interviews between June and September 2021. Interviews lasted 21 to 62 minutes, and were audio recorded and transcribed verbatim. No additional interviews were conducted once content saturation was reached.

2.4. Analysis

We used rapid qualitative analysis, which is emerging as a rigorous and efficient way to inform real-time implementation efforts.[22,23] Rapid methods were favored over traditional qualitative methods to speed delivery of the findings and inform clinician-facing messages as part of the broader project.[24] First, we developed a coding matrix based on the interview questions and DOI domains to summarize the transcribed data. Next, one author (AA) coded the first 15 transcripts using this matrix; the analytic team (including MH, AA, and MD) met to review the coding of these transcripts and evaluate suitability of the code domains; only minor modifications were made to the coding matrix. All remaining transcripts were coded using this matrix (by AA). Twelve transcripts (i.e., about one-third of the total interviews) were independently coded by an additional author (either MH or MD) to ensure intercoder reliability. We achieved 93% accuracy; all 7% of the coding discrepancies were found in 8 transcripts and resolved through discussion. Lastly, after independently reviewing all coded data, the team met to decide upon the most prominent themes.

2.5. Ethical considerations

The Colorado Multiple Institutional Review Board approved this study as exempt human subjects research (#21-2747), and participants provided verbal consent.

3. Results

We interviewed 38 clinicians from 16 Colorado counties. Interviewees were diverse in type (84.2% physician vs. 15.8% advanced practice providers, specialty (47.7% Family Medicine, 23.7% Internal Medicine, including Geriatrics), gender (50% Female), and clinical setting (34.2% community-based outpatients, 18.4% hospital-based outpatient, 10.5% Federally Qualified Health Centers). We recruited clinicians with a range of self-reported mAb knowledge and experience referring patients for mAb treatment, based on our statewide survey.[17] Interviewee characteristics are displayed in Table 1.

About one quarter of participants reported practicing in rural Colorado (26.3%; n = 10) and a quarter reported working in independent clinical settings not health care system-affiliated (26.3%; n = 10); only 5.3% (n = 2) practiced in independent settings in rural locations.

Tables 2 and 3 display facilitators and barriers to mAb referral and access, organized by DOI domain, with representative quotations.

3.1. Facilitators to referral, access, and equity

Nearly universally, clinicians reported the most significant attribute supporting mAbs was their perceived efficacy against severe

Table 1

Descriptive characteristics of interviewees in the mAb Colorado study.

Characteristic	Number	Percent
Total	38	100
Female	19	50
Race/ethnicity		
White	31	81.6
Black	1	2.6
Hispanic	2	5.3
Asian and Pacific Islander	4	10.5
Clinician type		
Physician: MD/DO	32	84.2
Other clinician: PA/NP	6	15.8
Faculty appointment in a medical school	14	36.8
Specialty		
Emergency medicine (incl. urgent care)	8	21.1
Family Medicine	18	47.7
Internal Medicine (incl. geriatrics)	9	23.7
Pediatrics	1	2.6
Infectious disease	2	5.3
Years since completing training		
<10	10	26.3
10–20	16	42.1
>20	12	31.6
Setting characteristics		
Clinical setting		
Emergency department	9	23.7
Outpatient, FQHC	4	10.5
Outpatient, community-based	13	34.2
Outpatient, hospital based	7	18.4
Inpatient	3	7.9
Long-term care facility	1	2.6
Other	1	2.6
Geography		
Urban	28	73.7
Rural	10	26.3
Health system affiliation		
Health-system affiliated	28	73.7
Independent	10	26.3
Self-reported mAb knowledge and referrals		
Level of knowledge about mAbs		
Know nothing	1	2.6
Know a little	12	31.6
Know a moderate amount	18	47.4
Know a lot	7	18.4
No. high-risk COVID-19 patients cared for in last month		
0	3	7.9
1–9	24	63.2
≥10	8	21.1
Not reported	3	7.9
Reported using CDPHE registry		
No, not at all	19	50
Yes, once or twice	6	15.8
Yes, three or more times	13	34.2

Characteristics obtained from a statewide survey of clinicians in Colorado.[17]

CDPHE = Colorado Department of Public Health and Environment, FQHC = Federally qualified health center, mAb = monoclonal antibodies.

disease and hospitalization from COVID-19, as well as an excellent safety profile. Notably, most clinicians did not perceive the Emergency Use Authorization status to be concerning, though some believed FDA approval might increase mAb acceptability among patients.

To learn about novel treatments for COVID-19, interviewees reported use of peer-reviewed journal articles; national-level sources were trusted for safety and efficacy information (e.g., peer-reviewed journal articles, CDC communications, clinical practice guidelines). Beyond these, clinicians thought specialty-specific information (e.g., emergency medicine podcasts, professional association newsletters) could be particularly influential. For communication about mAb referral systems and implementation processes, participants wanted to hear from their administrative or clinical system leadership. Indeed, leadership was perceived to exert a powerful influence over the adoption of mAbs. Unfortunately, clinicians in smaller, independent practices sometimes reported less access to these resources.

Translating mAb awareness to actual treatment relies upon implementation processes, including orders and referrals. For some, practicing in large, system-affiliated clinical settings was an asset for mAb access. Some large systems invested available resources into developing the streamlined processes many clinicians desired (e.g., automating the mAb ordering process, flagging positive cases in EHRs, and creating standing orders for outpatient treatment). Staff in non-clinical roles were seen as critical to establishing the process, workflow, and documentation. In general, processes that were more hands-off for

clinicians were described as facilitating access. However, this was not always the case – some clinicians from independent practice settings described how their close relationships with patients supported engagement and shared decision-making around mAbs.

A critical facilitator to mAb access was awareness of a positive test result. Testing early (positive within 10 days of symptom onset to qualify for mAbs) and having on-site mAbs were key. Test results accessible in one's own system or EHR increased awareness among both health system affiliated and independent practices, but this was not always available. Illustrating a workaround, some clinicians asked patients to contact them directly with positive tests to obtain a referral for mAb treatment.

Larger systems were also able to concentrate expertise, such as developing teams knowledgeable about mAb eligibility criteria to counsel patients. In times of high COVID-19 patient volumes, economies of scale allowed larger systems to allocate personnel and resources to streamline access pathways, including via proactive patient outreach, which not only helped maintain sufficient demand for doses and appointments but also helped overcome the barrier of relatively low patient awareness of mAbs. A lack of such economies of scale did not always hinder those in smaller practices, however; some saw value in being able to "change on the dime" to implement new processes rapidly (without the overhead of large organizations) amidst rapidly changing pandemic circumstances.

3.2. Barriers to referral, access, and equity

Some attributes of mAbs were seen as barriers to access. That mAbs required an hour-long infusion (prior to availability of subcutaneous formulations) was perceived as increasing patient hesitancy and presenting a logistical barrier to administration in many clinical settings. Clinicians desired an oral formulation or mode of administration that would be quicker and more acceptable to patients. Clinicians also described the difficulty, but importance, of identifying from among all eligible patients those at highest risk and most likely to truly benefit from mAbs. Understanding this was critical to justify pursuit of a referral process that was time intensive, requiring at times a phone call to an infusion center or emergency room during a busy clinic day; filling out a state registration form; creating a complex order set within the EHR; consulting with a local COVID-19 treatment expert; or some combination of these. The perceived need to delay vaccine boosters in patients who had recently received mAbs was also a barrier to referral.

Clinicians expressed frustration at the complexity of the mAb referral process, which changed frequently. Logistical barriers led to worries that patients were falling through the cracks. Resource constraints were more acute in smaller, independent practices that lacked time and personnel required to navigate the process from identification of eligible patients, to registering with the state, to locating and scheduling the infusion. Some were altogether unaware of state, regional, or organizational processes for patient referrals and lacked established communication channels; the unpredictability of case counts and future need made it difficult to prioritize investing time or resources in new, internal mAb referral workflows.

Awareness of a positive test was a significant barrier for clinicians to make a referral. As utilization of third-party testing sites (e.g., drive-throughs, pharmacies, home tests, etc.) increased, it became harder for clinicians to keep a handle on positive tests in the timely fashion needed for referral. In addition, fewer patients were tested when overall case rates were low.

Centralized processes for receiving mAbs at designated state, regional, and/or organizational sites – although efficient – were sometimes seen as barriers to mAb access for rural or independent practices, resulting in equity concerns for patients at these sites. Although patients in rural settings are accustomed to traveling for specialized medical care, clinicians reported that travel time was a barrier for patients whose symptoms were initially mild and who were uncertain if they might personally benefit from mAbs. Patient access to infusion sites was also reported to be limited by volume (both number of sites and available appointments) and availability of transportation for COVID-positive patients. In times of supply scarcity, centralized sites within larger health care systems restricted appointments for patients outside of their system. In some cases, not having a positive test result visible within a system meant mAbs would not be administered in that system. In rural communities, clinicians explained that COVID-19 testing acceptability (e.g., due to socio-political climate), availability, and timeliness were barriers.

Many clinicians in acute care settings (emergency departments/urgent care) supported the idea of testing and treating at the same time. However, patients occupying a room for the multi-hour duration of treatment preparation, administration, and cleaning was perceived to be a physical and financial burden. One clinician in a rural emergency department setting explained that the cost, effort, administrative requirements, time, and perceived burden to patients and staff were not balanced by sufficiently convincing evidence of mAb efficacy, except for the highest risk patients.

Finally, clinicians described concerns related to allocating limited resources. Most prominently, clinicians were concerned whether it was wasteful to focus on mAbs when their efficacy might be questionable against emerging variants. Some noted lack of clarity on cost to patients, clinics, and hospital systems. Respondents questioned the investment of time and money on mAbs for only incremental gains when there were alternative strategies (e.g., vaccine outreach) that might be more cost-effective and with greater reach and impact. Lastly, they noted that the politicization of COVID-19 led some patients to reject any treatment outright.

4. Discussion

This study showed clinicians in Colorado were optimistic about the benefits of mAbs for treatment of high-risk outpatients with COVID-19. However, they perceived mAb referral processes and systems to be time consuming and complex. These findings directly informed the state of Colorado's strategies for dissemination and implementation of mAb referral and treatment processes. Implementation of standing orders for state-run treatment sites, mobile mAb buses serving low-access communities, centralized processes through multiple health care systems, implementation blueprint and guidance for subcutaneous administration processes (a checklist now used state-wide), and statewide webinars for clinician education all resulted from communicating these findings, during our study, with local and state health department partners. These strategies were developed to leverage facilitators and overcome barriers identified through this study.

Even as subcutaneous mAbs and oral antivirals have become available that overcome some barriers to access, their relatively low initial uptake suggests an ongoing need to focus on implementation processes for COVID-19 treatments. Unfortunately, sporadic reporting about distribution of therapeutics has made monitoring of availability and equitable access difficult to track. It is unclear how widely outpatient therapeutics are currently being used.[25,26]

Our findings highlight possible tensions between increasing access while attending to equity within the constraints of limited resources and a rapidly changing pandemic. We found no one-size-fits-all solution to increasing access to mAbs. Facilitators to access in one setting (e.g., centralized delivery systems within a large, integrated system in an urban setting)

Table 2

Facilitators to referrals, access and equity of monoclonal antibodies for COVID-19 infection, organized by diffusion of innovation domains.

Attributes of mAbs as an innovation	
Relative advantage or disadvantage (mAb infusion)	**mAbs are effective:**
	"By receiving this treatment, it decreases your risk of progressing to severe illness… in such an uncertain time with an uncertain disease, if you have a safe treatment that can offer that much potential benefit I feel like that's almost a no-brainer." *(physician, urban, health system affiliated)*
	EUA is not a concern:
	"Having an EUA for monoclonal antibody, I don't think it's a hindrance to its use… unless I get more information that there's some reason that they're not being given full approval, to me, at this point, an EUA is just as good as just a full approval for anything." *(physician, urban, health system affiliated)*
Relative advantage or disadvantage (societal costs)	**mAbs are worth the cost:**
	"The outcomes with higher risk patients, there's less complications, less hospitalizations and death… because we're in a small community it's pretty easy to stress our hospital system 'cause we have only so many beds available." (*PA, rural, health system affiliated*)
Systems of communication and influence about mAbs	
Diffusion and dissemination (communication channels)	**Traditional sources of medical information still apply:**
	"I kind of scan the [JOURNAL 1] and [JOURNAL 2] and then I have [DISCIPLINE-SPECIFIC JOURNAL] that I look at regularly and kind of scan through the articles and things that kind of pertain. And then there'll be things that will show up there that I look into more. And also, UpToDate, we use that in our electronic health record." (*physician, rural, health system affiliated*)
	National guidelines matter:
	"I really love to see things within the guidelines, through the IDSA or NIH or CDC. I also like to see, you know, papers published in peer-reviewed journals." (*physician, urban, health system affiliated*)
	Specialty specific information is needed:
	"I think the most compelling comes from within the specialty itself. There's a particular group, it's a group that does a lot of third-party education stuff. They do a podcast and routine educational updates. And I'd say they are the most effective…they're a source that I trust quite a bit as do a number of other emergency medicine practitioners that I know." (*physician, urban, independent*)
Leadership	**Leadership is critical to influence adoption:**
	"I think a big reason that we were all on board was that at the beginning – we had good leadership...Like, if you don't have the supervisor who's going to support the work that needs to be done to make the clinic flow well...I just feel like providers aren't gonna get the information on how important it is. And they're not gonna be able to offer it to patients. So I really think leadership is the biggest thing." (*nurse practitioner, urban, health system affiliated)*
Characteristics of the implementation process for mAb referral and treatment	
Centralization	**Centralized systems can reduce the burden on clinicians.**
	"We already have the infusion center and order sets and everything, and that was pretty streamlined to just initiate that. And then-then the infusion center really took over contacting the patients and setting up the time for them to get their therapy, which was pretty cool. But yeah. If I was, like, in a private practice and not connected to a large university-based system –
	- um, I would hope that I would have probably done the legwork to contact who does this. How do I refer to the patients to you?." (*physician, urban, health system affiliated)*
	Centralization comes easily for integrated systems:
	"I mean, I would think that just the very size and just with the school and with the various different schools within the healthcare branch. I would think that there's every bit of, if not [ACADEMIC MEDICAL CENTER], then who?" (*physician, urban, health system affiliated*)
Complexity and compatibility of mAbs referrals	**The more the central process was used, the easier it became:**
	"I've done it more. And, even though I haven't done it that often, I kind of know kind of what I need to do. So the first few times it was more difficult. But now I know sort of, "Oh, if I do this, it'll just give me a green." *(physician, rural, health system affiliated)*
	"It took me one time to be like, oh, okay. I understand this process." *(physician, urban, health system affiliated)*
Linkage to testing	**Testing early and treating at the same time supports access:**
	"So, for this to work you need to catch them before they're really sick, which means that they need to think about it, and get tested early, and contact you." (*physician, urban, health system affiliated)*
	"The infusion's the issue. You know? That the people have to be able to come in for an infusion to get it...what we can do in the urgent care is if somebody comes in with symptoms, we get the rapid test right then and there and give 'em the infusion. They're already there." *(physician, urban, health system affiliated)*
Practice setting characteristics	
Structure of care (i.e., health system affiliation)	**Being in a health system can support adoption:**
	"I do think being part of a relatively robust system is helpful, because it's a system…if the system's adopting something, then you kind of take the approach, of not only has this been reviewed at a system level by multiple different people, but the system is doing it, so I sort have to get on board. So that is helpful in terms of new things getting accepted and implemented." *(physician, urban, health system affiliated*)
	Small rural or independent practices may have closer relationships with patients to encourage use:
	[Regarding information about mAbs] "Some – most of the patients – well my – in clinical setting, I think, a lot of patients do rely on – they rely on their trusted physician." (*physician, rural, independent)*
Readiness for implementation	**Large systems have greater capacity to implement changes:**
	"And then just, like, kudos to the [SYSTEM]. I don't know if they had research people doing this, or if they had somebody built in some EMR alerts? Two of the three patients had already been contacted outside of their visit with me by the infusion services, or somebody saying "Hey you might be a candidate for this." It gave them some information. So I thought that was really a cool thing for the system to do." (*physician, urban, health system affiliated*)

functioned as barriers in others (e.g., small, independent practices in a rural setting who were distant or disconnected from those systems). Promising practices from other state and local-area programs suggest the Colorado experience was not unique.[27] Four main lessons emerged that might improve state and institutional responses as the COVID-19 pandemic continues and for future emergencies requiring rapid access to novel therapeutics.

First, testing must be directly linked with strategies to facilitate access to treatment.[28] Efforts to improve access to COVID-19 testing were not typically carried out with linkage to treatment in mind. This might have been because testing

Table 3

Barriers to referrals, access and equity of monoclonal antibodies for COVID-19 infection, organized by diffusion of innovation domains.

Attributes of mAbs as an innovation	
Relative disadvantage (mAb infusion)	**The mode of administration is a concern:** "Gosh, it's an infusion. That sounds complicated and hard. And if they don't know about the subcutaneous piece…And it's, I understand, uncomfortable – to have that much medication delivered into your subcutaneous tissue. By the fourth injection, people are getting a little tired of it." *(physician, rural, health system affiliated)*
	Infusions are complex to implement: "It's the time, and increased burden to both the patient, and to my ER, and the patients that are able to do it. I guess I have yet to see the solid evidence to say, 'Yes. We need to really do this for you.' If a person is willing to do it, I'm happy to give it to them. But I'm not going to try and strongly persuade them. Because I just – like I said, it's just that all of those seem like big barriers where I'm not really convinced that the adverse sides outweigh the benefits." (*physician, rural, health system affiliated)*
	Receiving mAbs may delay vaccination and boosters: "The concern is, you know, if you're giving them the antibody externally… how much will that delay if they need a third dose… a booster dose of the vaccine? Because if I – the booster dose and they have antibodies circulating at high levels, it may not be that effective, right? So now I'm saying, "Okay, well you got this. You probably should wait for your booster for 90 days. Let the antibodies go away and then get the booster." " *(physician, urban, health system affiliated)*
	Safety risks are rare, but not negligible: "One patient that we had, she came in with an anaphylactic reaction after receiving the antibody therapy… She came in probably every, about every other day over the course of a little over a week needing epinephrine. It was one of the things that – it really opened up my eyes to it… maybe just think a little bit more… These antibodies are still in the body for so long. It's not metabolized or broken down as quickly as medication is, and so if you do develop an anaphylactic reaction, it's gonna stick around for quite some time." *(physician, urban, health system affiliated)*
Relative disadvantage (societal costs)	**Resources may be better spent elsewhere:** "I don't know how much the monoclonal antibodies cost. Well, I don't know how much is the cost to the patient; how much our charge is; if it's being paid for by the state. I honestly have no idea about any of that information. But from an overall societal standpoint, I guess I assume that [mAbs are] relatively expensive, and it does concern me a little bit that we're spending money on them for not a huge gain. Whereas there are other things that we could spend that money on that may be more helpful. I mean, the vaccines, I think, are even more efficacious than the antibody treatment…So it almost makes sense, you know, a zero-sum situation to say, 'Well, if we're gonna spend a dollar either on monoclonal antibody treatments or on vaccine outreach, it seems like it would be a better use of the money to get people vaccinated.'" (*physician, urban, independent*)
Systems of communication and influence about mAbs	
Diffusion and dissemination (communication channels)	**Finding relevant and timely information is still a challenge:** "It's one of those things that it's sort of similar to, like when HIV and-and AIDS came about, and we just didn't know a whole lot about it. So things just got deferred to the high-level specialists who were handling that. Right? The family practice just sort of said, 'We don't really know a whole lot, so we're just going to not touch this.' And that's-that's sort of where are we – I think that's sort of what's happened with COVID. It's just sort of been, like, we don't know enough. And it's a lot to navigate." *(PA, urban, independent)*
Leadership	**Leadership may need more support to promote mAbs:** "And I could imagine that if our leadership had the right, like, contacts and information and felt motivated to do it, and felt like it was important, we could do, like mass text message campaigns and update our Instagram and Facebook accounts to be like, ""We have treatment for COVID. FYI, call us." *(physician, urban, FQHC)*
Characteristics of the implementation process for mAb referral and treatment	
Centralization	**Centralized systems may not be trusted:** **"**Saying wow...we can make this easier by just having, Joe Smith from Denver call Betty Sue in rural Colorado and say, "Hey, I'm Joe Smith, I see that your COVID test is positive." Betty Smith is gonna go, "What? How do you know my test is positive?" That's the first response. And then, "Who are you?...and you're now telling me that I should go to this location to get some test or some treatment that I've never heard about? Okay, goodbye...I'm gonna go call my primary care physician. So you know, even though I hear that system is maybe being slick and simple, it is not patient-centric....Their language is, 'How do I feel? Do I trust you? I don't even know what questions to ask, so I need to go to my trusted person...'" (*physician, rural, independent)*
	Centralized systems may not benefit all equally: "We probably had three or four patients that did qualify, none of them wanted to travel to the hospital. So, the system probably was not unreasonable, it was too onerous for us and our patient population" (*physician, rural, independent*)
Complexity and compatibility of mAbs referrals	**The referral process is too complex:** "Getting a patient enrolled as a candidate has been too difficult to do. It takes a lot of additional time for myself in addition to obviously the time we spend at the office visit. If the staff is involved in doing it, they don't all of the sudden have the technical knowledge to be able to do that themselves. And so, sometimes if they're asking us questions. So, it kind of bogs us down a little bit in terms of trying to get that set up." (*physician, urban, independent*)
Linkage to testing	**Being unaware of test results can delay access to treatment:** "I think the first barrier is just getting people tested." (*nurse practitioner, urban, FQHC)*
	"I try to get 'em to [my health system]...as opposed to-to these days going to, you know, the Walmart and getting a rapid COVID test that they take at home. And so the – whether they're positive or negative, we'll never know." (*physicians, urban, health system affiliated)*
	"….in [northern Colorado city] where they would get tested, or they'd be in Walgreens or something or – that was probably the - the hardest part to try and get the results of that test." (*physician, rural, independent)*

(*Continued*)

Table 3
(*Continued*)

Practice setting characteristics	
Structure of care (i.e., health system affiliation)	**Large systems can sometimes be slow:**
	"I often feel frustrated that things are slow – they're really slow to change in these big systems, and I have no idea how to improve that… There's also just other stuff with government regulations and how hospitals are supposed to approve new ideas that it's just a slow, lengthy process. If you have a new idea or a new drug that you want to use, it has to go through multiple committees for approval. I'm not super familiar with how all that works, but I just know it takes a long time." (*physician, urban, health system affiliated*)
	Rural systems may not have capacity to support new processes:
	"So yeah. I think the barriers to bringing [mAbs] to a rural place like [RURAL LOCATION], Colorado would be, do we have the numbers to make it reasonable to bring that into our hospital, and how does insurance cover it? Will patients be receptive to another, like, new, scary – essentially a thing that they're unsure of. So I don't know." (*physician assistant, rural, independent*)
Readiness for implementation	**On the frontlines, it can be difficult to incorporate new tasks:**
	"I think a big barrier is figuring out how to incorporate these infusions in with the regular flow of the clinic now that the volume is picking up… trying to figure out how to get all your other work done – how to get all your other patients seen and still be doing these infusions at the same time… It's a barrier." (*nurse practitioner, urban, health system affiliated*)
	A lack of interoperable systems can be a barrier:
	"[To get access to mAbs] I asked my medical assistant to fax over the enrollment form, and then I received a phone call from the pharmacist, I think, from the infusion center who essentially said, 'I can't accept this order by fax, but if you sign-in to [EHR] and you open' – I'll make a chart for this patient. Like, I'll open a chart for this patient… 'cause they didn't exist in the [EHR] before…" (*physician, urban, FQHC)*

capabilities emerged months before treatment options became available. Home testing, while improving access to testing, may exacerbate this challenge. Home tests do not include information on how to obtain treatments, and home test results may not be visible to clinicians or the state or health system to facilitate outreach, thus delaying engagement with health care providers.

Directly linking infectious disease testing and treatment is not a novel problem, and lessons from hepatitis C and HIV[29,30] may apply for COVID-19. The Biden administration's federal "Test to Treat Initiative" aims to establish "one stop" testing and treatment distribution in pharmacy-based clinics.[28] However, distribution in pharmacies is limited to oral antivirals and implementation of the program has been halting. State, local, and health system efforts will still be needed to link testing to treatment. Because treatment selection requires consideration of efficacy, convenience, patient baseline health status, and time from symptom onset, continued investment in systems supporting testing and treatment integration for mAbs and other therapeutics is warranted.[31] Emergence of new COVID-19 variants has continually rendered some treatments obsolete, while new products enter the market. Halting of HRSA's Uninsured Relief Fund and commercialization of mAbs introduced cost considerations that were not present before 2022 for some providers and patient populations. In future COVID-19 surges or pandemics, testing should be conceived of in linkage to a flexible array of treatments from the outset – even if treatments do not yet exist.

Second, centralized systems for testing and treatment are efficient and may improve delivery of novel therapeutics but need to be sensitive to issues of equity. The experience with mAbs demonstrates that it is possible to increase aggregate use of a novel therapeutic while exacerbating underlying disparities in access for underserved groups.[32] Rural clinicians in our sample reported informational, geographic, and trust barriers to their patients using centralized, state-level or integrated systems. In these settings, access to treatments through primary care was perceived to be more effective and equitable.

Encouraging models of local centralization may help harmonize the strengths of the diffuse and centralized systems that have emerged to date.[33–36] Such models could build broader networks connecting independent settings to one another or to existing centralized systems. Alternatively, defining a geographic catchment area that reduces the coverage areas of large systems to a smaller radius with less stringent "own patient" requirements may be another way to improve access and equity. Colorado did this, in part, when it launched mobile bus mAb treatment sites, which traveled to underserved areas of the state and eventually allowed patient self-referral for treatment.[37]

Third, ongoing innovation of treatments and their delivery are needed and can sometimes improve access and equity. With mAb treatments, for example, the development of subcutaneous administration was seen as a critical innovation for expanding access. As experience with mAbs grew, and the risk of anaphylaxis was found to be very low, availability of subcutaneous injections administered outside infusion centers and by trusted local clinicians overcame barrier to access in rural areas and in home health. Authorization of shelf-stable, oral formulations has contributed to additional gains in equitable access, especially in more rural areas.

However, innovative treatments are unlikely to overcome all barriers; innovative and creative delivery solutions are also needed. In one example, a local health system facilitated broader access in urgent care settings by administratively re-categorizing mAb infusions as injections – thus treating them more like an IV antibiotic routinely given than a "special" new infusion.[38–40] Additional innovations will be critical to bring access to COVID-19 therapies to other patient population (e.g., home health patients, health care shortage areas, people experiencing homelessness).

Fourth, accurate and timely communication from trusted sources is key. During COVID-19, information changes so rapidly that clinicians are not always able to turn to their most trusted sources of information (peer-reviewed journal articles, clinical practice guidelines) because those sources are not always current. Local communication channels, including clinical and system leadership, have become more critical and in some ways more trusted.

Avoiding and correcting "first impression" bias (i.e., the idea that people weight heavily the first piece of information they receive) turned out to be an important lesson. Initially, Colorado publicized using a random allocation system for mAbs, anticipating that demand would far exceed supply. This created a first impression that mAbs were in short supply, which influenced clinician referrals for many months. At the time of our interviews, there was ample supply of mAbs, but some clinicians (especially in independent settings) were under the impression that Colorado was using the random allocation system that, in fact, had never been activated (instead functioning as a connector tool for infusion facilities with available appointments and as a statewide monitoring system). Investment in strengthening trusted local sources of information with specific attention to strategies for changing information will remain important for the duration of the COVID-19 pandemic and for future public health emergencies.

4.1. Limitations

There are several limitations to this study. First, as a qualitative study of Colorado clinicians, our findings do not necessarily generalize to clinicians in other states and policy contexts. Second, while we conducted surveys and focus groups with patients and families,[18] this analysis does not include these perspectives. Patient-perceived facilitators and barriers may be different than those experienced by clinicians. Third, although we sought a diverse sample based on geography and clinical setting, we did not achieve significant representation for some ethnic and racial groups. While participants reflected clinicians in Colorado generally, there may be unique barriers associated with race or ethnicity of clinicians or their patient populations that we were unable to identify. Lastly, Colorado experienced relatively low COVID-19 case during summer 2021 when our interviews were conducted, and vaccines were widely available. Breakthrough infections among vaccinated individuals were believed to be relatively rare and concentrated among people who were immunocompromised. As new information about vaccine efficacy over a longer-term and for new variants (e.g., omicron) has emerged, clinician perceptions may have also shifted. Finally, interviews were completed while the overall project was iteratively developing clinician- and community-based messaging campaigns, informed in part by these findings, beginning in July 2021. Thus, our findings reflect clinician perspectives as elements of the mAb messaging campaign were rolled out.

5. Conclusion

As COVID-19 is poised to become endemic, the need to connect patients from a positive test to effective treatments in an efficient and timely manner will persist. No matter the treatment, additional investments in the systems and processes necessary to make this connection are needed in responding to this or the next pandemic. Further engaging end-user stakeholders, including frontline clinicians, will also be critical for the design of systems that address their unique facilitators and barriers.

Author contributions

Conceptualization: Mika K. Hamer, Bethany M. Kwan, Matthew K. Wynia, Adit A. Ginde, Matthew W. DeCamp.
Data curation: Mika K. Hamer, Ahmed Alasmar, Matthew W. DeCamp.
Formal analysis: Mika K. Hamer, Ahmed Alasmar, Matthew W. DeCamp.
Funding acquisition: Bethany M. Kwan, Matthew K. Wynia, Adit A. Ginde.
Investigation: Mika K. Hamer, Matthew W. DeCamp.
Methodology: Mika K. Hamer, Matthew W. DeCamp.
Project administration: Ahmed Alasmar.
Software: Ahmed Alasmar.
Supervision: Bethany M. Kwan, Matthew W. DeCamp.
Validation: Mika K. Hamer.
Visualization: Mika K. Hamer, Ahmed Alasmar.
Writing – original draft: Mika K. Hamer.
Writing – review & editing: Mika K. Hamer, Ahmed Alasmar, Bethany M. Kwan, Matthew K. Wynia, Adit A. Ginde, Matthew W. DeCamp.

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