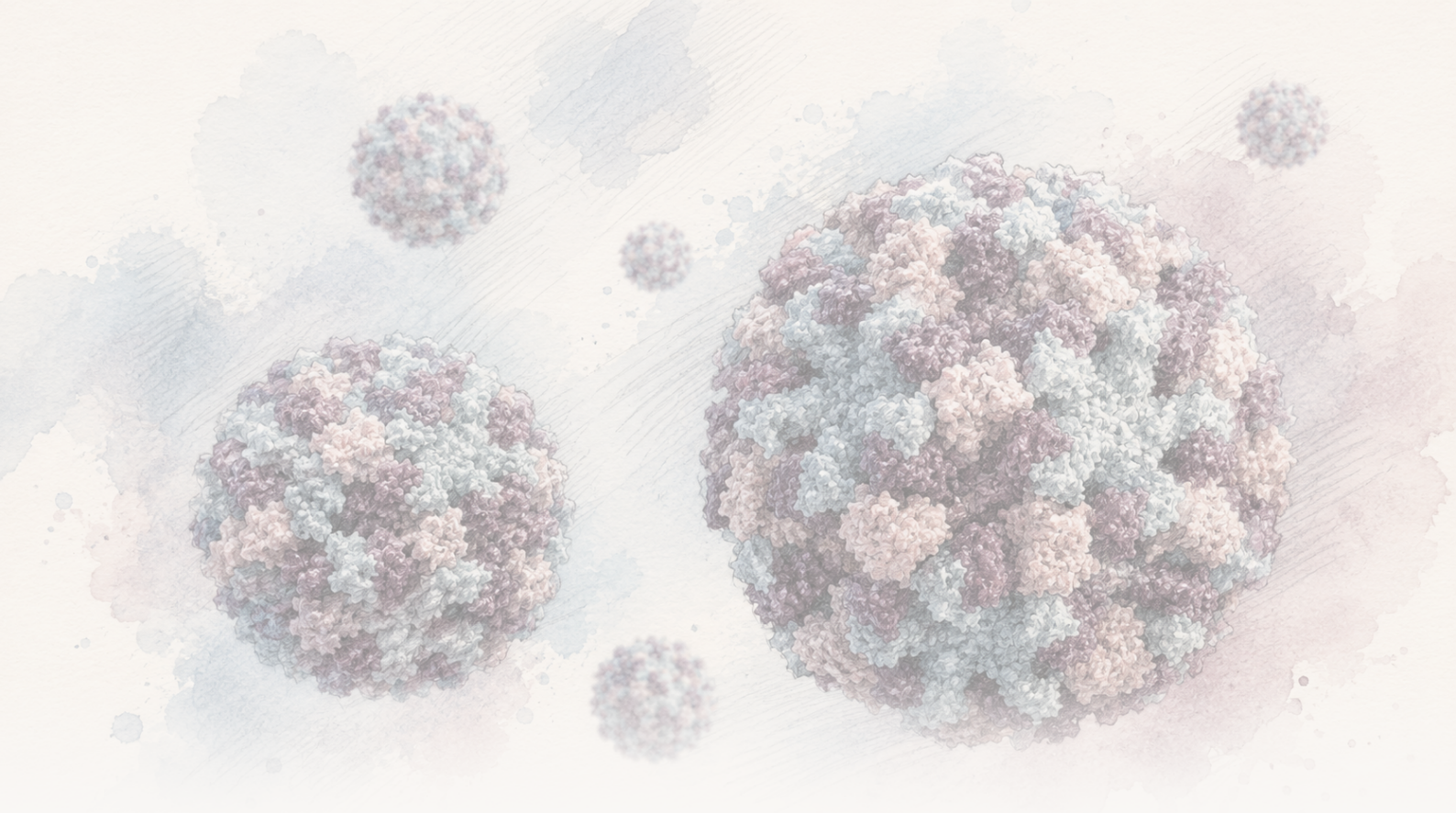

The Clean Paper

WHAT THE PAPER SAYS · WHAT IT DOESN'T · WHY IT MATTERS

# Oral norovirus vaccine ya rage infection a challenge trial — amma ya miss clinical endpoint ɗinsa

*Phase 2b human-challenge study ya gwada oral tablet vaccine against GI.1 norovirus. Vaccinated adults sun fi karancin qPCR-detectable infection bayan challenge, sun nuna mucosal immune responses, kuma sun shed less viral RNA a wasu time points. Amma prespecified clinical gastroenteritis endpoint ba a meet ba, trial ya yi controlled high-dose challenge a healthy adults, kuma bai measure real-world transmission ko protection against currently dominant GII.4 genotypes ba. Promising step ne toward norovirus vaccine, ba proof cewa ya iso ba.*

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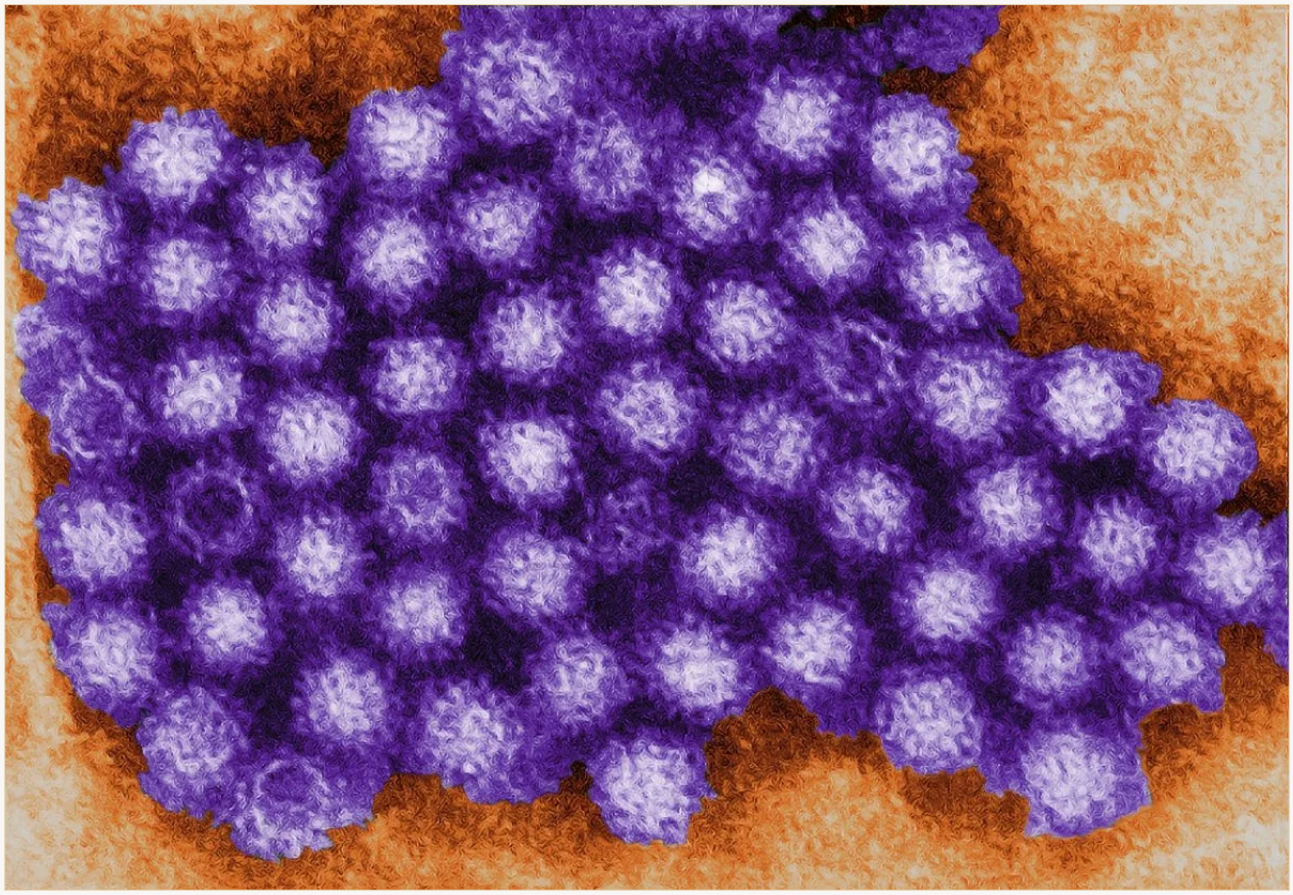
Paper: *An oral norovirus vaccine generates mucosal immunity and reduces viral shedding in a phase 2 placebo-controlled challenge study*, Becca A. Flitter, Joshua Gillard, Susan N. Greco, Maria D. Apkarian, Nick P. D'Amato, Lam Quynh Nguyen, Elena D. Neuhaus, Darreann Carmela M. Hailey, Marcela F. Pasetti, Mallory Shriver, Christina Quigley, Robert W. Frenck Jr., Lisa C. Lindesmith, Ralph S. Baric, Lee-Jen Wei, Sean N. Tucker & James F. Cummings, Science Translational Medicine (2025) · DOI: 10.1126/scitranslmed.adh9906

# Gwajin challenge hanya ce mai amfani ta samun amsa da wuri, amma ba ƙarshen tafiya ba

Norovirus shi ne kwayar cutar da mutane da yawa suka sani ta hanyar wata mummunar ciwon ciki da ke zuwa ba zato ba tsammani: amai, gudawa, ciwon ciki, da kwanaki kaɗan na rashin lafiya mai tsanani. Yana yaɗuwa cikin sauƙi a wuraren da mutane suke raba iska, saman abubuwa, banɗaki, abinci da kulawa — makarantu, gidajen kula da tsofaffi, asibitoci, sansanonin soja da cibiyoyin kula da yara. Har yanzu babu rigakafin norovirus da aka ba lasisin amfani.



Hoton norovirus virions da CDC ta ɗauka da transmission electron microscope kuma aka ƙara masa launi. Binciken da ake tattaunawa a nan ya gwada ɗan takarar rigakafi na baki a gwajin challenge mai sarrafawa da norovirus GI.1.

CDC / Charles D. Humphrey Public domain

Saboda haka wannan binciken yana da ban sha'awa sosai. Marubutan sun gwada rigakafin kwaya da ake sha, VXA-G1.1-NN, a gwajin challenge na mutane na bazuwar rarrabawa, tare da placebo. An yi wa manya rigakafi, sannan aka fallasa su da gangan ga norovirus GI.1. Rigakafin ya rage kamuwa da cuta da qPCR zai iya gano wa, ya haifar da martanin garkuwar jiki a jini da mucosa, kuma a wasu lokuta ya rage RNA na kwayar cutar a bayan gida da amai.

A gwajin challenge na mutane, fallasar ba ta faru ne bisa kuskure ba. Ana yi wa masu sa kai masu lafiya rigakafi ko placebo, sannan a ba su ƙayyadadden adadin kwayar cuta da gangan a wuri mai cikakken kulawa. Wannan tsarin

yana iya gano alamar tasiri da sauri, amma ba daidai yake da kallon yadda rigakafi yake aiki a barkewar cuta ta yau da kullum ba.

Amma sakamakon ba ya nufin cewa “rigakafin norovirus ya zo.” Abin da ya nuna ya fi ƙanƙanta kuma ya fi amfani: a tsarin challenge na phase 2b, ɗan takarar rigakafin baki ya nuna raguwar kamuwa da cuta mai muhimmanci a kididdiga da kuma wasu alamomin garkuwar jiki da ka iya alaƙa da kariya, **amma bai kai babban ma’aunin asibiti da aka kayyade tun farko na gastroenteritis ba**. Bai tabbatar da kariya a rayuwar yau da kullum ba. Masu rigakafi sun sami ƙananan lokuta na gastroenteritis na norovirus, amma bambancin bai isa ya zama tabbataccen sakamakon asibiti ba. Binciken kuma bai gwada nau’ikan norovirus da suka fi mamaye shekarun baya-bayan nan ba.

Wannan bambanci yana da muhimmanci. Gwajin challenge yana iya bayyana alamar tasiri da sauri fiye da gwajin da ake yi a cikin jama’a. Haka kuma yana iya taimaka wa masu haɓaka rigakafi su gano alamomin garkuwar jiki da suke tafiya tare da kariya. Amma ba zai maye gurbin hujja mafi wahala da ake buƙata kafin a ba rigakafi lasisi kuma a yi amfani da shi a yawan jama’a ba.

## The primary clinical endpoint comes first

*The trial showed a promising infection signal, not a vaccine-arrived result.*

| | | |
|---|---|---|
| PRIMARY NOT MET | **Norovirus gastroenteritis**<br>44.7% vaccine vs 56.9% placebo; P = 0.178 | Clinical endpoint: symptoms + qPCR infection |
| SIGNAL SIGNIFICANT | **qPCR-detectable infection**<br>57.1% vaccine vs 81.5% placebo; P = 0.003 | Broader measure: viral RNA detected by qPCR |
| FUTURE GUIDANCE | **Candidate correlates**<br>Fecal IgA + serum blocking antibody predict infection status | Useful for later trials; not licensure evidence |

Takaitaccen hoton bita: babban ma’aunin gastroenteritis da aka kayyade tun farko shi ne na farko kuma ba a kai shi ba; raguwar kamuwa da cuta da qPCR ya nuna ta kasance mai muhimmanci amma ma’auni ne mafi faɗi; alamomin garkuwar jiki hanya ce ta tsara gwaje-gwajen gaba, ba hujjar cewa rigakafin ya shirya don amfani ba.

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# Abin da marubutan suka yi

Tawagar ta gudanar da gwajin phase 2b a wuri guda, wanda aka ɓoye wa mahalarta da masu bincike rarrabuwar rukuni, aka rarraba mutane bazuwar lokaci, kuma aka kwatanta rigakafi da placebo. Mahalarta manya ne masu lafiya masu shekaru 18 zuwa 49. An ba su ko dai kwayar rigakafin baki VXA-G1.1-NN ko placebo.

An shigar da **mutane 165**: 86 a rukunin rigakafi da 79 a rukunin placebo. Bayan rigakafin, an ba **mahalarta 141** norovirus GI.1 mai rai ta baki a matsayin challenge: 76 daga rukunin rigakafi da 65 daga placebo.

Gwajin ya bi tambayoyi biyu masu alaƙa.

Na farko: shin rigakafin ya rage shaidar gastroenteritis na norovirus bayan challenge? Babban ma'aunin inganci da aka kayyade tun farko ya haɗa abubuwa biyu: alamomin da suka cika ma'anar acute gastroenteritis **da** shaidar kamuwa da norovirus ta qPCR. A sauƙaƙe, ba gwajin kwayoyin halitta mai kyau kaɗai ake buƙata ba; dole ne mutum ya yi rashin lafiya kuma gwajin ya nuna kamuwa da cuta.

Na biyu: shin rigakafin ya haifar da alamomin garkuwar jiki da za su taimaka wajen bayyana kariya? Marubutan sun auna antibodies a serum, IgA na mucosa a bayan gida, ruwan hanci da miyau, ƙwayoyin da ke fitar da antibody, plasmablasts masu komawa mucosa, RNA na kwayar cuta a bayan gida da amai, da kuma samfuran machine learning da suka nemi alamomin da ke alaƙa da kariya.

A nan ne darajar tsarin gwajin take. Ba kawai binciken "mutane sun yi rashin lafiya ko a'a?" ba ne. Yana kuma tambayar wane irin martanin garkuwar jiki zai iya zama muhimmi ga haɓaka rigakafin norovirus a gaba.

# Abin da suka gano

Ba a kai babban ma'aunin asibiti da aka kayyade tun farko ba. Gastroenteritis na norovirus ya faru a **44.7%** na rukunin rigakafi da **56.9%** na rukunin placebo. Bambancin maki **12.2 na kashi** ne, ko raguwar dangi ta **21%**. Amma confidence interval ya haye sifili (95% CI -4.24 zuwa 28.61), kuma sakamakon **bai kai muhimmancin kididdiga ba** (P = 0.178). Lokacin tsara gwajin, marubutan sun yi tsammanin bambanci mafi girma: kusan 40% gastroenteritis a placebo da 12% a masu rigakafi. Abin da aka gani ya tafi a alkiblar da ake tsammani, amma bai kusanci wannan zato na farko ba.

Alamar inganci mafi ƙarfi ta fito ne daga **kamuwa da cuta da qPCR ya gano**, wanda ma'auni ne mafi faɗi kuma mai sassauci fiye da gastroenteritis na asibiti. Bayan challenge, **57.1%** na masu rigakafi suna da kamuwa da norovirus da qPCR ya gano, idan aka kwatanta da **81.5%** a placebo. Bambancin ya kai **maki 23.6 na kashi** (95% CI 7.4 zuwa 38.0, P = 0.003), wato raguwar dangi ta **30%**.

Wannan jerin sakamakon shi ne muhimmin abu. Rigakafin ya rage kamuwa da cuta da za a iya ganowa a wannan tsarin challenge. Haka kuma rukunin rigakafi ya sami ƙananan lokuta na gastroenteritis na norovirus, amma rashin tabbas ya yi yawa har ba za a kira wannan tabbataccen sakamakon asibiti ba. A harshen kididdiga, gwajin bai kai babban ma'aunin asibiti ba. Ya kamata a riƙe waɗannan gaskiyoyi biyu tare.

Bayanan aminci sun ba da kwanciyar hankali, amma suna da iyaka. Marubutan ba su ga wani serious adverse event da aka danganta da rigakafin ko dose-limiting toxicity ba. Yawancin adverse events da aka nema kai tsaye bayan

rigakafi sun kasance masu sauƙi, kuma ba a ruwaito wani mai tsanani a makon farko ba. Maganar da ta dace ita ce rigakafin **an jure shi da kyau a wannan gwajin**, ba cewa an riga an warware duk tambayoyin aminci masu wuya ko masu matuƙar wuya ba.

Martanin garkuwar jiki ya kasance mai faɗi. Zuwa rana ta 28, idan aka kwatanta da placebo, rukunin rigakafi yana da VP1-specific IgA da IgG a serum da kuma functional blocking antibody titers mafi girma. Haka kuma VP1-specific IgA ya ƙaru a bayan gida, ruwan da ke rufe hanci da miyau. A jini, rigakafin ya motsa antibody-secreting cells da mucosal-homing plasmablasts — irin martanin da ake son rigakafin mucosa da ake sha ya haifar.

Sakamakon yawan fitar da kwayar cuta ma yana da amfani, amma yana da sauƙin wuce gona da iri wajen fassara shi. RNA na kwayar cutar ya ragu a amai a rana ta 2 bayan challenge, kuma ya ragu a bayan gida a ranaku 4 da 8. Yawan mutanen da qPCR ya nuna suna da cuta amma ba su da alamomin acute gastroenteritis ya kasance 13.1% a rukunin rigakafi da 24.6% a placebo, amma wannan bambancin bai kai matakin muhimmancin kididdiga da aka saba amfani da shi ba (P = 0.087). qPCR yana gano **RNA na kwayar cuta**; wannan ba daidai yake da auna kwayar cuta mai iya yaɗuwa kai tsaye ba.

# Me ya sa alamomin garkuwar jiki suke da muhimmanci

Haɓaka rigakafin norovirus yana da wata matsala ta aikace-aikace: manyan gwaje-gwajen da ake yi a cikin jama'a suna da wahala. Barkewar cuta na da gajeren lokaci, ba a san lokacin zuwanta ba, kuma tana taruwa a wasu wurare. Idan masu haɓaka rigakafi ba su san wane irin martanin garkuwar jiki yake hango kariya ba, yana da wahala su yanke shawarar waɗanne 'yan takara suka cancanci kuɗi da girman gwaje-gwajen gaba.

Saboda haka ɓangaren binciken da ke neman **alamomin da ke alaƙa da kariya** yana da muhimmanci. Marubutan sun horar da samfuran lissafi da bayanan garkuwar jiki daga mahalarta masu rigakafi kafin challenge. Abubuwa biyu sun fi bayyana: **serum blocking antibody** da **fecal IgA**. Na farko yana auna yadda antibodies ke hana kwayar cutar ɗaurewa a gwajin dakin bincike; fecal IgA kuwa alamar antibody ce da aka auna a bayan gida, kusa da saman hanji inda norovirus yake aiki.

Samfurin Lasso ya hango matsayin kamuwa da cuta da AUC 0.76; random forest ya samu AUC 0.73. AUC ma'aunin aikin samfurin ne: 0.5 ba zai fi sa'a ba, 1.0 kuma zai raba rukunan ba tare da kuskure ba. Darajoji kusan 0.73–0.76 suna da amfani amma ba su da ƙarfi har su zama hukunci. Suna nuna cewa waɗannan alamomin garkuwar jiki sun taimaka wajen bambance waɗanda suka kamu da waɗanda ba su kamu ba a wannan binciken. Ba su samar da sabon gwajin tantance cuta ba, kuma ba sa juya gwajin challenge zuwa hujjar da ta isa lasisi.

Suna dai nuna cewa haɗin functional serum antibody da IgA na hanji na iya taimakawa wajen hango wanda rigakafin zai kare.

Wannan ya dace da ilimin cutar. Norovirus yana kamuwa ne da saman mucosa. Rigakafin da ake sha yana ƙoƙarin gina kariya a inda kwayar cutar ke shiga da ninka kanta, ba a jini kawai ba. Saboda haka saƙon binciken da ya fi ƙarfi game da tsarin kariya ba "kwayar rigakafi ta magance norovirus" ba ne. Shi ne cewa **garkuwar mucosa — musamman fecal IgA tare da functional blocking antibody — ta yi kama da muhimmiyar hanya da za ta jagoranci mataki na gaba na haɓaka rigakafi.**

# Abin da wannan binciken bai tabbatar ba

- Bai nuna cewa an amince da rigakafin norovirus ko yana samuwa ba. Wannan gwajin challenge ne na phase 2b.
- Bai tabbatar da kariya a rayuwar yau da kullum ba. An yi amfani da challenge mai sarrafawa, ba fallasa ta dabi'a a makarantu, gidajen tsofaffi, asibitoci, jiragen yawon buɗe ido ko gidaje ba.
- Bai tabbatar da kariya daga duk norovirus ba. An yi challenge da GI.1; GII.4 ya fi yaduwa a cikin shekaru ashirin da suka gabata.
- Bai sa ƙananan yawan gastroenteritis ya zama tabbataccen sakamakon asibiti ba. Raguwar kamuwa da cuta ta qPCR ta kai muhimmancin kididdiga; babban ma'aunin gastroenteritis bai kai ba.
- Bai tabbatar cewa rage fitar da RNA yana hana yaɗuwar cuta ba. Gwajin ya auna RNA a samfurori, ba yaɗuwar cuta daga mutum zuwa mutum ba.
- Bai warware tambayoyin aminci masu wuya ba. Ba a ga wata babbar matsala da aka danganta da rigakafin ba, amma wannan ba babban kundin bayanan aminci ba ne.
- Bai kawar da batun rikicin muradu ba. Vaxart ce ta ɗauki nauyin binciken, kuma marubuta da dama ma'aikatan Vaxart ne, masu hannun jari, masu ba da shawara ko masu riƙe da patent.

Waɗannan iyakoki ba sa soke sakamakon. Suna bayyana girman abin da sakamakon zai iya faɗa.

# Muhimmin ƙuntatawa na tsarin challenge

Marubutan sun bayyana wani babban iyaka kai tsaye: a gwajin challenge ana zaɓar adadin kwayar cuta da zai sa isassun mutane su kamu domin nazarin ya samu ƙarfi. A takardar, sun ce irin waɗannan gwaje-gwaje masu sarrafawa kan yi amfani da adadin kwayar cuta mai kamuwa da cuta da ya fi fallasar dabi'a ta yau da kullum da **umarnin girma uku zuwa biyar**. *Inoculum* shi ne adadin farko na kwayar cutar da ake ba mahalarta; a nan an ba su ƙayyadadden adadin Norwalk virus GI.1 mai rai ta baki.

Wannan yana da fa'ida da illa.

A gefe guda, tsarin yana da ƙarfi. Yana ba masu bincike damar gwada rigakafi cikin kulawa, tare da sanin lokacin fallasa, nau'in kwayar cuta, yawan samfurorin da za a ɗauka da kuma martanin garkuwar jiki kafin da bayan challenge. Wannan shi ya sa binciken zai iya faɗa abubuwa da yawa game da kamuwa da cuta, fitar da kwayar cuta da alamomin kariya.

A gefe guda, tsarin na wucin gadi ne. Babban adadin challenge na iya mamaye wasu kariyar garkuwar jiki ko ya canza alaƙar da ke tsakanin kamuwa da cuta da alamomin rashin lafiya. A wannan binciken, attack rate na kamuwa da cuta ta qPCR a placebo ya yi yawa — kusan 82% — yayin da attack rate na gastroenteritis ya yi ƙasa, kusan 57%. *Attack rate* a nan yana nufin rabon mahalarta a rukuni da suka sami sakamakon da ake dubawa. Marubutan sun ce ƙananan yawan cutar asibiti na iya rage ƙarfin gwajin gano bambanci a gastroenteritis. Sun kuma lura cewa ba a san ko alamomin hanji a challenge sun samo asali daga ninkawar kwayar cuta mai rai ba, daga babban inoculum ɗin da aka bayar, ko daga duka biyun ba.

Saboda haka karatun da ya fi taka-tsantsan ba "rigakafin yana aiki ne kawai da wannan kaso" ba ne, kuma ba "zai fi aiki a wajen challenge" ba ne. Abin da za a ce shi ne: **gwajin challenge gwaji ne mai tsauri kuma mai yawan**

**bayani, amma sakamakonsa har yanzu yana buƙatar tabbatarwa a cikin jama'a.**

## Me ya sa wannan yake da muhimmanci

Abu ne mai sauƙi a juya wannan labari zuwa: kwayar rigakafi ta rage norovirus, don haka rigakafin "stomach bug" ya kusa zuwa. Wannan ya wuce abin da shaidar ta nuna.

Labari mafi amfani shi ne cewa haɓaka rigakafin norovirus na iya samun hanya mafi bayyananniya. Wannan ɗan takarar ya nuna raguwar kamuwa da cuta a gwajin challenge na mutane, ya haifar da martanin garkuwar mucosa, kuma ya nuna wasu alamomin garkuwar jiki da za su iya taimaka wa gwaje-gwajen gaba. Wannan ci gaba ne.

Amma har yanzu matakin farko ne. Abin da duniya ke buƙata ba rigakafin da ya yi aiki kawai a challenge na GI.1 a manya masu lafiya ba ne. Ana buƙatar hujjar cewa rigakafi zai kare mutanen da norovirus ya fi cutarwa — tsofaffi, yara, mazauna wuraren kulawa, marasa lafiya — da kuma a barkewar cuta ta gaske inda nau'ikan kwayar cutar suke canzawa.

Wannan takardar tana taimakawa wajen rage tazarar. Ba ta rufe ta ba.

## Takaitaccen bayani

Gwajin phase 2b na bazuwar rarrabawa tare da placebo ya gwada ɗan takarar rigakafin norovirus na baki VXA-G1.1-NN a manya masu lafiya. Bayan challenge da GI.1, babban ma'aunin gastroenteritis da aka kayyade tun farko ya faru a 44.7% na masu rigakafi da 56.9% na placebo — raguwar dangi ta 21% wadda **ba ta kai muhimmancin kididdiga ba**. Kamuwa da cuta da qPCR ya gano, ma'auni mafi faɗi, ya faru a 57.1% da 81.5% bi da bi, raguwar dangi ta 30% mai muhimmanci a kididdiga. An jure rigakafin da kyau a wannan gwajin; ya haifar da antibodies a serum da mucosa, ya rage RNA na kwayar cuta a wasu lokuta, kuma serum blocking antibody da fecal IgA sun fito a matsayin alamomin kariya da za a ƙara gwadawa. Sakamakon yana da kyau, amma ba rigakafin da aka ba lasisi ba ne, ba hujjar phase 3 ta rayuwar yau da kullum ba ce, ba tabbatacciyar raguwar yaɗuwar cuta ba ce, kuma ba hujjar kariya daga duk nau'ikan norovirus ba ce.

## Bincike ba tare da ƙarin gishiri ba

**Abin da takardar ta nuna:** A challenge mai sarrafawa da GI.1, ɗan takarar rigakafin baki bai kai babban ma'aunin gastroenteritis ba, amma ya rage kamuwa da cuta da qPCR ya gano, ya haifar da martanin garkuwar mucosa, bai nuna wata babbar matsalar aminci da aka danganta da rigakafin ba, kuma ya rage RNA na kwayar cuta a bayan gida ko amai a wasu lokuta.

**Abin da yake yiwuwa amma ba a tabbatar ba:** Wannan tsarin rigakafi zai iya rage yaɗuwar cuta ta hanyar rage fitar da kwayar cuta; fecal IgA da serum blocking antibody za su iya taimaka wa zaɓin rigakafin gaba; ko wani rigakafi mai nau'ikan antigens biyu zai iya rufe nau'ikan norovirus da suka fi muhimmanci a yau.

**Abin da bai nuna ba:** Cewa an amince da rigakafin norovirus ko ya shirya don amfani; cewa zai hana barkewar cuta ta gaske; cewa yana karewa daga GII.4; cewa gastroenteritis ya ragu da tabbacin kididdiga; cewa an auna yaɗuwa daga mutum zuwa mutum; ko cewa an warware tambayoyin aminci masu wuya.

**Manyan iyakoki:** Mahalarta manya ne masu lafiya; challenge ɗin nau'i guda GI.1 ne; an yi amfani da babban inoculum na wucin gadi; babban ma'aunin gastroenteritis bai kai ba; qPCR RNA ba daidai yake da kwayar cuta mai iya kamuwa ba; kamfani ne ya ɗauki nauyin gwajin kuma akwai rikicin muradu a tsakanin marubuta; babu hujjar inganci ta phase 3 a jama'a.

**Yawan amincewar da ya dace ga mai karatu na gama gari:** Babba cewa ɗan takarar rigakafin ya haifar da martanin garkuwar mucosa da ake nema kuma ya rage kamuwa da cuta ta qPCR a wannan challenge. Matsakaici cewa yana iya rage fitar da kwayar cuta kuma alamomin garkuwar da aka gano za su taimaka wajen haɓaka rigakafi. Kasa ga duk wani ikirari cewa rigakafin norovirus ya riga ya samu, yana karewa daga nau'ikan cuta da yawa, ko an tabbatar yana dakatar da yaɗuwa a rayuwar yau da kullum.

## Majiyoyi

Flitter et al., Science Translational Medicine (2025)
https://doi.org/10.1126/scitranslmed.adh9906

ClinicalTrials.gov, NCT05212168
https://clinicaltrials.gov/study/NCT05212168

Zenodo analysis code record, DOI 10.5281/zenodo.15178451
https://zenodo.org/records/15178451