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Eliminating Murine Norovirus by Cross-Fostering

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Murine norovirus (MNV) is a newly discovered and extremely prevalent pathogen of laboratory mouse colonies. MNV causes severe disease in some immunocompromised mouse strains and can cause persistent infections even in immunocompetent mice. Despite the fact that immunocompetent mice are generally asymptomatic, the possibility that MNV infection might alter immune responses makes its eradication a potentially useful goal for many facilities. Initial attempts by others to use a strategy of testing and culling were unsuccessful, whereas complete depopulation and facility decontamination was successful. However, these measures may be impractical, and finding less drastic approaches seemed prudent. Based on a report that cross-fostering of pups from MNV-positive mothers to MNV-negative ones could be successful in experimental MNV infection, we undertook a comprehensive fostering program using Swiss Webster mothers, careful sanitary measures, and fecal PCR testing to eradicate the virus from a mouse colony recently infected with MNV. We successfully decontaminated 17 of 18 (94%) litters and managed to prevent spread when a new MNV-infected mouse strain entered quarantine at our facility. These results suggest that cross-fostering, when performed in a setting of excellent sanitary procedures, may be practical for the large number of mouse facilities in which MNV is endemic.

Abbreviations: MNV, murine norovirus; B6, C57BL/6.

Noroviruses are important causes of viral gastroenteritis in humans. Approximately 50% of all human cases of epidemic gastroenteritis, including many outbreaks on cruise ships, dining halls, and nursing homes, are caused by human norovirus.[3] Although the diseases caused by human and murine noroviruses differ in many respects, some of the challenges in eradicating the viruses from the environment are similar.

Murine noroviruses (MNV) were discovered recently [8] and found to be very prevalent in experimental mouse facilities, with 32% seropositivity among blood samples submitted to Charles River (Wilmington, MA) for testing, 10-fold higher than the next most common viral pathogen, mouse parvovirus.[6,11] Mouse strains with defects in innate immunity, such as STAT1$^{-/-}$/RAG1$^{-/-}$, IFNγR$^{-/-}$/RAG1$^{-/-}$, STAT1$^{-/-}$, and IFNα/βR$^{-/-}$/IFNγR$^{-/-}$ mice are much more susceptible than are wild-type mice.[8,12] With natural infection by MNV these mouse strains have dissemination of virus to the liver, lungs, and peritoneal and pleural cavities with associated inflammation.[8,12] Experimental intracranial infection leads to death in some of these immunodeficient mice.[8] In addition, RAG2$^{-/-}$ mice, which lack functional B and T cells, can have asymptomatic but persistent infection of mesenteric lymph nodes without disseminated tissue infection.[12]

One study[9] compared 2 procedures for eradicating MNV from their mouse facilities. One room was presumed to have limited MNV infection, and a culling and testing program was instituted. Cages of mice serologically positive for MNV were removed, as were cages of mice descended from positive mice or cages that contributed bedding to positive sentinels. Cages housed adjacent to MNV-positive cages tested negative, suggesting the possibility that the sanitary techniques were sufficiently stringent to prevent spread. However, by 4 mo, additional cages were MNV positive, either by serology or RT-PCR of fecal pellets, indicating a failure of this procedure. The authors of the cited study[9] suggested that environmental contamination likely was responsible for viral persistence, because biosafety cabinets and other possible fomites had not been decontaminated. In addition serologic screening may not pick up all MNV infection, allowing for persistence in mice.

The study's[9] second approach involved complete depopulation and extensive cleaning, including replacement of all disposable items, replacement of HEPA filters, as well as wiping of biological safety cabinets and rack motors with chlorine dioxide. This procedure was successful in ridding the room of MNV.

Unfortunately the successful procedure above is extremely disruptive to research and would involve great expense and the potential loss of irreplaceable mouse strains. Rederiving infected strains by embryo transfer is very expensive if many strains are involved. An alternative approach showed that methods of cross-fostering similar to that used to eradicate mouse hepatitis virus can be used for MNV.[4] Using experimental infection of Swiss Webster dams, the author[4] demonstrated that neonatal pups are not infected for the first 10 d of life and that pups from dams positive for MNV strain L and transferred to MNV-negative dams on days 1 through 6 remained negative. When 2-d-old litters were transferred from dams infected with MNV strain C, D, or G to MNV-negative dams, the procedure was successful in 17 of 19 attempts (89%). When pups became infected, the author[4] proposed that skin-contaminated pups acted as fomites to infect the foster mother and pups secondarily. Another study[2] extended this cross-fostering method to eradicate MNV from multiple mouse lines, as well as removing *Helicobacter* spp. and mouse hepatitis virus. The authors[2] determined that fostering was best performed by first transferring newborn pups and mother to a new cage and then transferring pups within 24 h to a foster mother. The success of cross-fostering has been questioned by authors who found that cross-fostering only changed prevalence from 51% to 22%, with 27% of strains (4 of 15) failing the fostering process.[13]

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In June 2007, a strain of mice that was MNV-infected was received into our rodent quarantine from another university. The sentinel from quarantine tested positive by serology. This mouse strain was introduced into our Biosafety Level 2 barrier room, 1 of our 3 rooms that had a negative history of MNV seropositivity since testing for the virus began in 2006. At 7 mo after transfer, MNV was detected in all 3 rooms by serology of sentinel mice. When individual breeding cages were tested by fecal PCR, all but 3 were MNV-positive. To eliminate MNV from these rooms, we pursued a regime of cross-fostering based on previously reported procedures.

Materials and Methods

Mouse colony. Our AAALAC-accredited mouse colony consists of 3 mouse rooms: 2 with stand-alone filter-topped microisolation cages and 1 with conventional, open cages and microisolation cages. The BSL2 room is 1 of the 2 barrier rooms. We also have several other rooms that are used for other species, such as rabbits and rats, and rooms that are used for quarantine or storage. Thirteen transgenic and knockout strains, mostly on a C57BL/6 (B6) background, are bred inhouse. All animals from nonapproved vendors are quarantined before entry into the main mouse population.

Husbandry. Most purchased wild-type mice were housed in open caging. Genetically engineered mice and the Swiss Webster mice used for fostering, whether purchased or bred inhouse, as well as mice infected with experimental pathogens (BSL2), were housed in microisolation caging. Bed o' cobs (The Andersons, Maumee, OH) mixed with pine shavings (NEPCO, Warrensburg, NY) bedding (1/8 in.), Lab Rodent Diet 5001 (PMI, Richmond, IN), and tap water (nonacidified) were used for nonsterile cages. For immunocompromised mouse strains, caging and water were sterilized by autoclaving, and irradiated PicoLab Rodent Diet (PMI) was used. Food and water were provided ad libitum. Cages were changed weekly, and water bottles changed semiweekly. Enrichment included a nesting square (Nestlets, Ancare, Bellmore, NY) and rodent shelter (Shepherd Shelter, Shepherd Specialty Papers, Watertown, TN) or transparent mouse retreat housing (BioServ, Frenchtown, NJ). Washed cages, after assembly and with enrichment items and cage card holders, were autoclaved by using transparent plastic bags that were tied shut. Full water bottles were autoclaved separately in sealed autoclave bags; bottles were added when mice were placed in caging or for water bottle replacement. Cages were sanitized in a cage and rack washer using detergent (Cage Klenz 180, Steris, St Louis, MO). A biologic hood or changing hood was used for cage manipulations.

All animal use was according to IACUC-approved procedures and protocols, and all mice were generated for use in approved protocols.

Sentinel program. The sentinel program used 4-wk-old female CD1 mice (Charles River Laboratory, Wilmington, MA). The singly housed sentinel was exposed to soiled bedding for 12 wk (quarterly). A pinch of soiled bedding (approximately 12 g) from at least 6 cages was placed into a clean cage of bedding (185 g of bedding). Sampling of caging was taken horizontally across or vertically downward. Only one sentinel was used for each rack or side, and all cages were sampled systematically. After 3 mo, live sentinels were sent for testing using Charles River Research Animal Diagnostics Services' Mouse Tracking Profile (serologies for mouse parvoviruses 1 and 2, minute virus of mice, and NS1; mouse hepatitis virus; MNV; Theiler murine encephalomyelitis virus; mouse rotovirus; Sendai virus; pneumonia virus of mice; reovirus; *Mycoplasma pulmonis*; and as a control, for the presence of IgG). A parasitology examination for ectoparasites and endoparasites was performed for lice, mites, *Aspiculuris tetraptera*, *Syphacia muris*, *Syphacia obvelata*, fecal ova and cysts, *Chilomastix* spp., *Entamoeba* spp., *Giardia* spp., *Hexamastix* spp., *Monocercomonoides*, *Retortamonas* spp., *Spironucleus* spp., and trichomonads. In addition, PCR assays for mouse parvovirus (mesenteric lymph node) and MNV (fecal pellets) were performed.

Quarantine. Mice entering the facility from nonapproved vendors, such as other universities, were quarantined in a separate room with a sentinel. While in quarantine, mice were maintained in microisolation, sterile, or nonsterile caging, as appropriate for the mouse strain. Personnel wore protective clothing, including disposable gown, gloves, mask, hat, and doubled booties. All cage manipulations were performed in a biological safety cabinet with soiled cages bagged and sprayed with disinfectant (Virkon S, Pharmacal, Naugatuck, CT) before exiting the room. Everything bagged was autoclaved before entering the washroom area for sanitation. After the quarantine period was completed (4 wk), the live-sentinel animal was shipped to Charles River Laboratories for serology, parasitology, and PCR testing as discussed previously. If all screening results were negative, the mice were released to the main mouse rooms.

Sample collection and MNV testing. Fecal pellets (the freshest available) were collected from mice by using autoclaved forceps (2 pellets per cage) and placed in sterile microfuge tubes. In some cases, pooling was performed (10 pellets per sample) on sets of 5 cages in a single room. Fecal samples from the litters were sent to Charles River Laboratories for commercial MNV PCR testing 3 to 4 wk after fostering, with confirmatory retesting of these cages at 6 to 8 wk after fostering.

Sanitary procedures. The following procedures were instituted in July 2008, as part of the cross-fostering protocol. Investigators don booties when entering the facility. Animal facility personnel wear dedicated work boots that do not leave the facility, instead of putting booties on street shoes. Disposable gowns, gloves, bouffant hats, masks, and an additional set of booties are put on when personnel enter the animal room and are removed on leaving the room. New protective clothing is donned for entering a new room. Hands are washed with soap and water before gloves are put on and after glove disposal. The MNV-negative room is dealt with first, and quarantine rooms are always dealt with last in a given day, without entry into other rooms afterward by those personnel. Cages are changed in a biological safety cabinet that was wiped down with 1% Virkon S before and after use; the product remained on the surfaces for at least 1 min before being wiped away. Cages with mice are wiped with Virkon S prior to placing them in the hood. Autoclaved forceps are used to pick up mice and are dipped in Virkon S between cages. Cages and bedding were bagged in autoclavable decontamination plastic bags that were tied shut; the bags were wiped with Virkon S and autoclaved. At the start of the decontamination program, all disposable items including markers, pens, tape, and so forth were replaced with new, uncontaminated ones. All instruments were autoclaved or thoroughly wiped down with Virkon S. All surfaces of the room were cleansed with Virkon S 3 times over 3 d. Laminar flow hoods were wiped down thoroughly with Virkon S, removable parts were washed, and HEPA filters were replaced.

Cross-fostering. Swiss Webster outbred mice (6 to 8 wk old) were obtained from Taconic Farms (Germantown, NY) and bred in house in our MNV-negative room, with breeding triads set up on a staggered basis, several days apart, to ensure the availability of litters when needed. Taconic Farms is an MNV-

negative facility. Swiss Webster dams were used within 5 d of littering. MNV-positive dams (that had come from known fecal PCR-positive cages) and their pups were transferred to a new autoclaved cage on day 1 after birth of their litters; on the next day (day 2 of life), these litters replaced litters of pups from MNV-negative mothers. One of the Swiss Webster pups was retained along with the transferred pups to help with acceptance of the new pups (but was not used specifically for testing). This Swiss Webster pup was distinguishable by coat color.

Two people performed the actual transfer. One person worked under the hood in the MNV-contaminated room and removed pups from the MNV-positive mother at 2 d old, setting pups on a paper towel lightly sprayed with Virkon S and then placing pups into a clean sterilized transfer cage. The identification of the pups was recorded on the transfer cage card. Gloves were decontaminated with Virkon S, and the outside of the cage was wiped with Virkon S. This person then degowned and exited the room, carrying the transfer cage to the door of the MNV-negative room and passing the cage to the second person.

This second person worked under the hood in the clean room, removing the MNV-negative Swiss Webster foster dam and one pup from her cage to another sterilized cage. The identification of the foster female was recorded on the cage card. Donated pups were placed into the new home cage keeping all of the pups together. The identification of the pups was recorded on the foster female cage card. All handling was done gently. The transfer cage was placed in a decontamination bag, tied shut, and removed for autoclaving. Care was taken not to contaminate the fostering room with any objects from contaminated rooms, with cages autoclaved before introduction. Testing was performed twice on each cage (at 3 to 4 wk and 6 to 8 wk) before mice were released to a clean room, where caging was autoclaved before use. Various mouse strains were cross-fostered until all mouse strains were decontaminated; all remaining MNV-positive mice were euthanized, and terminal cleaning was performed on the MNV-contaminated rooms by spraying all surfaces with Virkon S 3 times on 3 consecutive days before using the animal room as a clean room.

During fostering of different strains, mice that were negative for MNV were housed in a clean animal room and had cages changed on different days of the week from the contaminated rooms. A schedule for the order in which rooms were to be entered for daily observation and care of the animals was established, with cleanest rooms entered first, followed by contaminated rooms, and finally the quarantine room, if occupied.

After MNV had been eliminated, a new strain of mice (B6.129 Jα18$^{-/-}$) was introduced to quarantine and found to be positive for MNV by fecal PCR assay. One litter of this mouse strain was cross-fostered by using an available B6.129 FcγRI$^{-/-}$ foster mother rather than a Swiss Webster dam. This case was successful and is included in Table 1.

Results

MNV initially was detected in one strain of mice that was transferred from another university in June 2007. Our mouse facility had tested negative for MNV (by our sentinel testing program) since 2006, when Charles River Diagnostics added serology for MNV to their panel of pathogens tested. Spread within the colony to all 3 rooms occurred within 7 mo, by January 2008. All breeder strains and cages tested positive for MNV by fecal PCR assay, except for 3 cages of one strain (B6.129 FcγRIII$^{-/-}$). This outcome underscores the difficulties in preventing the spread of MNV from cage to cage and room to room. Table 1 shows the 13 mouse strains that underwent cross-fostering. In our initial attempts, we were successful with 16 transfers and unsuccessful with 1; this failure was detected at the fecal PCR test at week 3 or 4. These mice were euthanized, and the cross-fostering room was cleaned terminally as described earlier. We tried a second time with this strain and succeeded. We had a total success rate of 17 of 18 (94%). Fostering took place from July 2008 until August 2009.

Discussion

MNV is a newly identified pathogen with unclear implications for research. Several groups have not found changes in infection outcome of mice with Friend retrovirus,[1] murine cytomegalovirus,[5] vaccinia virus,[7] and influenza A virus.[7] However, inflammatory bowel disease induced by *Helicobacter bilis* in Mdr1a$^{-/-}$ mice was altered by MNV infection.[10] MNV is very prevalent, and because of its potential effect on immunologic studies, research institutions may choose to exclude it from their colonies. The methods available at this time include rederivation by embryo transfer, as is performed by large mouse vendors such as Jackson Laboratories, Charles River, and Taconic Farms. This method has the advantage of the likely removal of unknown, as well as known, pathogens. However, this procedure is costly if many strains of mice need to be decontaminated. An alternative is to cross-foster pups soon after birth to MNV-negative foster mothers as first tried in experimental MNV infection in a previous study.[4] The results of this method on infected colonies have been mixed: one laboratory[2] found great success whereas another did not;[13] our efforts occurred before the cited work[13] was published. In our hands, Swiss Webster foster dams successfully reared all litters, and in only one case did MNV transfer to the litter. This strain subsequently was fostered successfully.

The reasons for the discrepant results may be multifactorial. First, the discrepancy may lie in differences in MNV strains (not determined by us or reported in the previously cited studies[2,13]), given that the inoculum needed for infectivity or the amount of shedding may vary among different viral strains. Other authors had better success with fostering MNV strains L and C than strains D and G, although chance cannot be excluded.[4] Second, mouse strain differences (pup strains and surrogate strains) may matter. Some authors[13] hypothesized that immunocompromised mouse strains may not cross-foster very successfully, although the basis for this opinion was not discussed. The 4 failures among the 15 strains attempted were not defective in innate immunity, which is known to increase susceptibility to MNV. In addition, one previous study[2] involved 19 immunocompromised strains (including IFNα/βR-deficient mice) that fostered well (5 failures among 287 attempts), as did we. Of course, specific immune defects may be the deciding factor.

In any case, the strains of mice in each facility will vary and therefore fostering would need to be tried empirically. Our group and one previously[2] used Swiss Webster mice as surrogate mothers; another[13] used ICR mice. Unfortunately we could find no published studies comparing infectivity of MNV between these 2 mouse strains. Furthermore, one study[13] exclusively used serology, rather than PCR testing, to diagnose MNV. In fact, one group[2] had a single foster mother that tested negative by serology at 4 wk, but the pups tested positive (based on fecal PCR) at 12 wk. We cannot discern whether this outcome was due to delays in seroconversion or an actual delay in infection. As one laboratory[13] recognized, their NOD/SCID and NOD/SCID. IL-2gr$^{-/-}$ mice would not have antibody responses. Therefore, if serology is the only basis for MNV diagnosis, these mice could

Table 1. MNV testing of fostered litters

Strain of the fostered litter	no. of MNV-negative litters / total no. tested
B6.129 IgG1−/−	2/2
B6.129 CD1d−/−	1/1
B6;129 AID+/+	1/1
B6;129 AID−/−	1/1
B6.129 Fcer1g−/−	1/1
B6.129 lck$^{cre/?}$ IL-10$^{flox/flox}$	2/3[a]
B6.129 Lyz2$^{cre/cre}$ IL-10$^{flox/flox}$	3/3
B6.129 ILK$^{flox/flox}$	1/1
B6.129 SCAP $^{flox/flox}$	1/1
B6.129 M-ILK$^{flox/flox}$	1/1
B6.129 Bak−/−	1/1
B6.129 FcγRI−/−	1/1
B6.129 Jα18−/−	1/1
Total	17/18 (94%)

Litters were tested for MNV by fecal PCR at 3 to 4 wk and retested at 6 to 8 wk after fostering.
[a]One litter became infected with MNV (lck$^{cre/?}$ IL-10$^{flox/flox}$) and was detected at the 3- to 4-wk test.

have occult infection and recontaminate the colony. If B-cell–deficient mice such as SCID or RAG$^{-/-}$ mice are present in the colony, these mice need to be tested by PCR assay. At times, PCR fecal testing may be positive before seroconversion, and this early warning may be important in stemming an outbreak. Although PCR assays may be more expensive, obtaining fecal samples for PCR testing may be easier to accomplish than would be survival bleeding of mice for serology.

Sanitary procedures are crucial. One previous study[13] did not describe the sanitary measures used to prevent contamination from room to room or cage to cage and reported only that ICR foster mothers and pups were moved to "a separate area." We put foster mothers with transferred litters into a separate room with careful precautions, including autoclaving all caging that entered, and another group[2] explained the changes needed in sanitation for successful fostering. Both groups[2,13] attempted to rid facilities of multiple pathogens including *Helicobacter* spp. and therefore we cannot explain outcome differences due to this multifaceted approach. Because MNV can survive on fomites,[6] care must be taken to remove or clean all contaminated equipment. The rapid spread within our facility prior to decontamination efforts underscores this fact. Finally, we are faced with relatively small numbers of mice. We had 1 failure in 13 strains (18 litters), whereas the previous studies had 5 failures in 19 strains (287 litters)[2] and 4 failures in 15 strains (number of litters was not published).[13] Perhaps these results represent experimental variation rather than truly different results. Given that pups do not become infected early in life, failures are most likely due to skin contamination of pups passing MNV to the foster mother, which then infects the litter over time from fecal–oral exposure. Although our Swiss Webster dams came to our facility from an MNV-negative vendor and care was taken to prevent any spread of MNV to these mice, we cannot rule out the possibility that the one cross-fostering failure stemmed from infection of the dam from fomites rather than from the transferred pups.

After eradication of MNV from our mouse population, another MNV-infected mouse strain entered our colony quarantine in July 2010 from another university's facility. In this instance, we had a B6.129 FcγRI$^{-/-}$ foster mother available and succeeded in cross-fostering a single litter in this way. This fostering was included in the overall numbers mentioned earlier and in Table 1. This success suggests that exclusion of MNV-positive mice can be accomplished by using cross-fostering, provided that quarantine procedures are performed very carefully.

In conclusion, we were successful in removing MNV from 13 strains of mice, some of which had immune defects, although none was severely immunocompromised. We recommend attempting cross-fostering by using Swiss Webster mice as foster mothers and with exquisite care taken not to spread MNV between cages and rooms. All potentially contaminated items, including biological safety hoods, pens, measuring devices, mouse holders, and so forth, need to be replaced or decontaminated by autoclaving or with appropriate disinfectants such as Virkon S. An important potential problem is the contamination of the newborn pups, which can infect the foster mother and then the litter in turn. Care may need to be given to disinfecting the pups' skin if frequent failures occur. We included a step in which pups were placed on a paper towel sprayed with Virkon S. Two extra rooms are desirable, one for the newly fostered mice and one used only for mice that test negative after repeat testing. Furthermore PCR testing is sensitive and superior to serology in mice that have B cell defects, such as SCID, μMT$^{-/-}$, RAG1$^{-/-}$, and RAG2$^{-/-}$ mice, which lack B cells and therefore antibodies. In addition, PCR testing may reveal MNV before seroconversion and therefore may shorten the time that infected mice are in a facility, decreasing the chance of spread from these mice. Our study did not identify any limitations or roadblocks that prevent successful cross-fostering of genetically engineered mouse pups on SPF mice for elimination of MNV.

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