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AN OVERVIEW OF VACCINATION IN FARM ANIMALS

Introduction to Part I: Emphasis on Field Problems under Difficult Conditions

by Earle Goodman, DVM

This issue is the first of a two part series on vaccination in farm animals with an emphasis on field problems under difficult conditions. The in-depth feature article which begins the series is followed by shorter articles in the second issue by well-known farm animal veterinary practitioners and a number of abstracts containing related information. Though animal vaccination has long been one of the most important aspects of disease prevention worldwide, there is still much confusion, lack of information and misinformation, especially regarding the practical aspects that still unfortunately and tragically lead to poor results. This series has been one of our most requested and has long been in its development because of the difficulty of locating authors who were able to discuss the subject from both the technical and practical aspects.

Vaccinology – Field Application

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***Note**: CVM extends our sincere appreciation for Dr. Ramirez's major effort to make this comprehensive overview of a very technical subject into an article that is both readable and practical.*

As veterinarians involved in world health, our role is to maximize the health of animals, especially livestock, so as to maximize the opportunities for a wholesome and safe food supply for the ever growing human population. In the perfect world, our vaccination interventions would occur in healthy animals two to four weeks before exposure occurs and we would be armed with a "perfect" vaccine. It is the purpose of this article to help bring forward some of today's knowledge on vaccination handling and techniques so as to maximize the results of our interventions in the not-so-perfect world. This information is not all inclusive, but rather serves as a framework from which to work.

The purpose of vaccination is to provide an animal with a controlled exposure to antigen(s) to allow for the development of an immune response which will prevent infection, minimize disease consequences, and/or minimize disease spreading (shedding). The results of vaccination are dependent on the organism of interest, the species involved, as well as the vaccine used.

Some vaccines such as *E. coli* in cattle are designed to prevent infection while others such as swine influenza in pigs are designed to minimize the consequences from infection and do not prevent infection. These differences are important and as veterinarians we need to take an educational role with our clients in the field as most expect vaccination to be a full protection measure. If there is a misconception on these objectives, compliance can become a critical issue.

Even with a perfect vaccine not all animals respond to immunization equally. These individual differences relate to the animal's health status, genetics, environmental factors, concurrent infections, as well as other unknown causes.

When a swine respiratory outbreak occurs we can still end up losing one or two pigs, but the key is that we are probably protecting many others. Dropping a vaccination program because it is not 100% effective is unrealistic not only in veterinary medicine but human medicine as well, where the stakes are even higher. A 1996 summary of human influenza vaccine effectiveness in the elderly from the University of York, United Kingdom, indicated that although it ranged from 49 to 69% effective, it was still considered quite effective. According to the U.S. Centers for Disease Control and Prevention the 2005-2006 human influenza vaccines were closer to 70-90% effective in healthy adults less than 65 years old. These figures help to reiterate that vaccines do not have to be 100% effective to be beneficial.

Although there are many areas of vaccination that are out of your control, there are others you can have an impact on especially when looking at vaccine handling and administration techniques. Through proper handling and administration of vaccines, you will be able to maximize the opportunity for the best immune response by the host and hopefully provide protection that may minimize the consequences of infection and therefore maximize animal health.

The Cold Chain

Maintaining proper cold chain (keeping vaccines refrigerated at all times) is challenging even under ideal situations. There are many steps involved from the production of a vaccine until it is finally administered to an animal in the field. At any one step the vaccine can be exposed to an adverse environment which can impact the effectiveness of a vaccine. Although it may seem to be a lost cause, there are definitely some basic principles that are crucial in helping mitigate these consequences.

When looking at vaccine handling there are two critical issues related to temperature and light (UV light) exposure. The magnitude and length of time of exposure are both critical and for the most part are additive for the life of the vaccine product. The threshold for when a vaccine has become inactive or is not worth using any more is not well defined.

Temperature

When looking at temperature exposure there are two issues to highlight. First we are concerned about killing the vaccine in the case of MLV (modified live virus/bacteria) vaccines, where immunity depends on the survival of the antigen in the vial to self replicate in the host. Different organisms have different susceptibilities to temperature variations.

There are also differences between vaccine manufacturers. MLV vaccines are much more sensitive to these higher temperatures than killed vaccines. There are a few instances that even killed vaccines can be affected by high temperatures. Even though killed vaccines cannot be "killed" further by high temperatures, these products can in fact be affected by high temperature exposure. High temperatures can denature some of the proteins in the vaccine or cause lysis of whole cells releasing endotoxins into the medium, both of which can cause a significant change in an animal's immune response to the administration of the vaccine. Bacterial contaminations, especially in the case of opened multi-dose vials, usually thrive with higher temperatures. This buildup in bacterial contamination can result in abscess formation or the

accidental death of an animal or group of animals. The issue of how to properly work with multi-dose vials will be addressed in another part of this article.

UW Light Exposure

Exposure to light (specifically UV light) is only a concern with MLV products. UV light serves to kill organisms (good method for sterilization) and thus can inactivate a MLV vaccine. Because MLV vaccines rely on replication of the organism in the host to induce immunity, the low antigen load in MLV vaccines will not be effective in inducing an immune response. An amber or brown color bottle is an excellent indication that a particular product is especially sensitive to UV light. The color in the vial serves to filter out UV radiation. These colored bottles are much more expensive than the clear bottles, so companies usually only use them on products were the UV protection is needed. The same is true regarding cardboard packaging. The purpose of the added boxes is not only to keep the diluent and freeze dried product together, but also protect it from UV light.

Possible Cold Chain Solutions

Magnitude and duration of time exposure both work together against the vaccine, so try to control at least one of them if possible. When storing and transporting vaccines, find the coolest, darkest area possible. The dashboard of a vehicle is probably one of the worst places to transport vaccines. Insulated boxes or containers can still insulate products from higher outside temperatures even when there is no ice in them. If possible, minimize the heat challenge that they are exposed to. Minimizing how often and how long these containers are opened and exposed to the outside environment will have an impact on their effectiveness in insulating vaccines. Finding or digging a hole in the ground can also serve as a starting point for storing vaccines. The deeper the hole is, the cooler the ground temperature.

Water can also be used as a means to dissipate heat and protect vaccines. Storing vaccines in plastic bags (two or three layers of sealable bags would be recommended) and immersing them in water will minimize their exposure to high temperatures. The surrounding liquid will absorb and redistribute the heat thereby requiring a longer time of exposure before the internal vaccine temperature is raised. The volume of water will have a direct relationship to the amount of heat that can be absorbed. This water can be replaced with fresher colder water as frequently as needed. Even if the water may seem to be warm, it is probably colder than the ambient temperature the vaccine will be exposed to. This water does not have to be potable since the vaccine vials will be protected from contamination by the plastic bags. Although this water technique can add significant weight to the transport of the vaccine, it can be used to protect vaccines during transport. Keep vaccines covered and in the shade to protect from UV light as well.

Using these general concepts will allow you to be creative on how to better manage your vaccine storage. Remember this is not an all or none process, but rather an additive process towards maximizing the potency of the vaccines under less than ideal real life conditions by minimizing exposure to heat and UV light.

Vaccine Administration

Now that we have maximized the potency of vaccines, we need to focus on the proper handling of vaccines as they are administered.

Syringes and Dosage

A clean accurate syringe is a must. The best way to clean syringes and needles is to use plain potable water. The use of soap, alcohol, or any other disinfectant can leave a residue on the syringe or needle that may inactivate MLV products. Use warm or preferably hot potable water and rinse the syringe with the needle multiple times. This is especially important to be done as soon after use as possible to minimize the chances for the drying or buildup of vaccine. Allowing the syringe and needles to completely dry is also important. If only killed products are used, then you can clean with soap or disinfectants, just make sure the next time you use that syringe it is not used with an MLV product. Because it is easy to forget what syringes and needles you used with what vaccine, it is best to treat all your equipment as if it was always going to be used next with MLV products and only use potable water for cleaning.

Automatic syringes must also be periodically checked for accuracy. The best way to do this is to fill up the syringe with plain potable water, set the dial to your usual setting (2ml or 5ml), and administer ten repetitions into a container that can be measured. Measure the total volume and divide by the number of repetitions. Repeat this procedure twice for each dose you use. The simple changing of ratchet gears can restore your syringe to accurate functionality. Administering the proper dose is critical to allow a proper immune response. Overdosing usually only increases your cost per animal treated and under-dosing may result in vaccine failure. Vaccines are approved based on specific requirements which are met based on the established dosage label.

Multi-dose Vials

Multi dose vials do pose a risk for accidental contamination. Some recommend the use of alcohol to swab the end cap before inserting your needle into the bottle. This seems to be a good practice but there are a few things to consider. To maximize disinfection properties you must allow contact time to occur. Ideally five minutes are recommended for alcohols, but simply waiting 30 seconds after wiping the bottle top is better than wiping and sticking your needle in right away. Also isopropyl alcohol is not effective against non-enveloped viruses so ethanol, if available, would be a better choice. You need at least 60 % alcohol and no more than 95% to be effective as a disinfectant.

To minimize contamination, ideally a new needle should be used every time you are to draw from a bottle. You should make sure to NOT inject air into the bottle but rather just draw out. Infecting air allows the opportunity for contamination to be introduced into the bottle. It is not recommended to leave a designated needle in a bottle. Leaving the designated needle in a bottle is like leaving the bottle open and exposed to the environment all the time.

If the multi-dose vaccine is a killed product, it is recommended that you write on the label the day you opened the bottle (first time you use it). The written date on the bottle will serve to remind you how "old" the bottle is. As you store this vaccine, the biggest risk is the opportunity for contamination to have occurred. That is why proper storage is critical. There are no established guidelines regarding how old of a product can still be used safely. Use your judgment based on how clean you feel the bottle is as well as how comfortable you are regarding the storage temperature of the product. Check the product for color changes, visual contamination, or the formation of precipitates, which all could suggest the product has been altered and is best to discard. Be careful to assume that just because you do not see physical changes in the product, does not mean it is not contaminated. If you have to use the product then it is best to use it in older, non-pregnant, healthier animals that are more likely to be able to fight off contamination.

If you have a 10 dose vaccine vial that you are drawing one dose over a longer period of time, it would be best to use a new needle (very important) and new syringe (if possible) each time. This will minimize the opportunity of contamination. Also remember to use the alcohol cleaning procedure described previously.

If using MLV products in multi-dose vials remember that once it is reconstituted, the live organisms have a limited life span. It is best to use the product as soon as possible. Unless you will be using the product that same day, you should discard it. MLV products rely on the live antigen to replicate in the host and stimulate the immune system. If by the next day you only have 10% viable organisms in the vaccine, the inoculating dose will not have the sufficient antigen load to stimulate an immune response. Some veterinarians may rely on mixing the old vaccine with new, but in reality this is exactly the same as adding distilled water to a new batch of vaccine which results in a diluted dose given to everyone. From a manufacturing standpoint, MLV vaccines require several logs less of organism as compared to killed products. This is because we rely on the MLV product replicating in the host to increase the antigen load. Killed products are formulated with a much larger antigen load and thus are generally more expensive to manufacture. So thinking that the old MLV vaccine has some killed organisms that will help with the immune response is incorrect. The total antigen load contributed by this MLV vaccine that is now killed is insignificant.

Mixing Vaccines

There is no clear cut answer to when it is okay to mix different vaccines in a syringe. Here are a few things to consider.

Technically, if you mix two products and do not get a chemical reaction in the syringe, it is probably okay to mix them in the field. If you are to mix products it is best to mix them on site immediately before they are used. If you store them mixed, it increased the opportunity for interactions, especially regarding proteins (which are our target immunogens), to occur. Binding, sequestering, or denaturing are all possibilities. All these chemical instabilities may lyse killed cells and alter their antigenic properties or alter adjuvant properties. It is best to not mix a killed product with a MLV unless they are known to be compatible, otherwise your MLV organism may be inactivated due to pH differences, preservatives, or other chemicals used in killed vaccines.

The real questions in mixing vaccines are not their chemical stability but rather their immunologic consequence. In addition to possible changes in antigen just discussed, combining too many vaccines can overwhelm the immune response resulting in only partial protection to some antigens but not all and we can not decide which antigens should get priority. This overwhelming challenge is practically the same whether we inject all antigens in one site or we use two separate injection sites. The challenge comes in that if we can combine vaccines the tendency is to keep giving more.

The swine influenza vaccine is a good example of mixing vaccines. When the first vaccines with H3N2 came out they were combined equal amounts with the traditional H1N1 vaccine. It was soon determined that the immune system was responding to one strain better than the other. To resolve the issue, vaccination protocols of 1/3 to 2/3 mixing combinations were developed to be more effective than the initial ½ to ½ mixing. Companies soon came out with multivalent commercial vaccines that contained the proper ratio of antigens to maximize the immune response to all strains.

Antigen overload is of special concern with gram negative vaccines which can contain varying levels of endotoxins. Too many endotoxins can cause animals to go off feed, run a significant fever, and even abort. So limiting the number of gram negative organisms used at one time may be helpful.

Needle Selection

The most important objectives when selecting needles are to deliver our vaccines to the proper site for maximum immune response while minimizing animal discomfort and maximizing cost effectiveness.

Technically one would use a longer needle for intramuscular injections and a shorter one for subcutaneous ones. We must also consider the age of the animal in selecting the right length. The gauge of the needle will mostly depend on the size of the animal and the toughness of their skin. Animals with tough skin require larger gauge (meaning smaller number) in order to minimize bending of needles. The following chart will help guide you to needle size and gauge selection when administering vaccines. Needle selections are based on my personal experience in combination with welfare recommendations by the different industry groups:

		Cattle	Swine	Sheep/Goats
Very Young	IM	16g x 1”	18g x ½”	18g x ½”
	SQ	16g x ¾”	18g x ½”	18g x ½”
Young	IM	16g x 1”	16g x 1”	16g x 1”
	SQ	16g x ¾”	16g x ¾”	16g x ¾”
Adult	IM	14g x 1”	14g x 1 ½”	16g x 1”
	SQ	14g x ¾”	14g x 1”	16g x ¾”

Intramuscular (IM), Subcutaneous (SQ)
Also see “A Note About Needles” following this article.

To economize many times I will only carry one needle size (IM size) and I will then adjust my administration technique for SQ injections as discussed in the next section.

When looking at the difference between stainless steel re-usable needles and disposables, I have found that disposables are much better. Today’s stainless steel needles do not keep their sharp edge as well as the old time needles. The lack of a sharp edge creates tension when injecting and predisposes those needles to easier bending and seem to be more painful to the animal. They also require a lot of maintenance with cleaning and therefore they minimize the chances of

contaminating multi-dose vaccine bottles. They also stay sharp, enabling them to be used on multiple animals. Having disposable needles also allows you to change needles between herds making sure you minimize the opportunity for blood borne disease spreading. These needles are also very economical today. In the U.S. you can buy a whole box of 100 needles 14g x 1" for $20 US. That is a low cost to pay for having a sharp needle and minimizing the chances of spreading disease.

Check your needles frequently for burrs (small bent tips) by looking at their tips as well as their ease of administration. If you feel you have to push that syringe a little harder to administer the vaccine, it is time to change needle. You should also consider changing the needle every time you have to refill your syringe with vaccine. This will minimize the opportunity for bacterial contamination to be introduced into multi-dose vials. One important issue with disposable needles is that when they bend, you must change the needle immediately. If you try and straighten the needle you will have weakened the base significantly and may end up breaking it in the animal next time.

Vaccination Location

It is recommended to vaccinate all food producing animals in the neck muscle. This will protect the more edible and valuable meat parts from incurring scaring or abscess formation. The proper location is anywhere in the neck ahead of the shoulder but behind a line drawn vertically from the base of the ears. The use of the rump area in all animals is discouraged primarily because of consumer concerns. The rump area includes some meat that is of high market values, especially in swine, that can be damaged or cause lesions from injections including vaccines. The more flexible and loose skin in the neck area also facilitates the administration of SQ injections. In the U.S., the current beef and pork quality programs strongly recommend the use of SQ injections over IM injections if possible to preserve meat quality. To administer SQ injections, angle the syringe so the needle is at a 15 degree to 45 degree angle to the neck. To give an IM injection, insert the needle perpendicular (90 degree angle) to the neck.

Animal Health

Reproductive Rate and Herd Immunity

Ideally all animals to be vaccinated should be in their best health in order to maximize their immune response to our vaccination. Unfortunately this is hardly ever the case. Our main goal with vaccination in livestock is to protect the herd first and then protect the individual. Most diseases have what is called a reproductive rate (R_0). That is the rate of new infections off from a single infected individual/animal. If the R_0 is greater than 1 then pathogen spread will eventually shut down as new infections are not occurring fast enough. Based on the R_0 for a particular disease, we can estimate the percent of the population that is needed to prevent pathogen spread. Although some pathogens do need close to 100% coverage in order to prevent an epidemic, most do not. In some cases even by achieving an 80% coverage rate we can in fact stop disease spread. This is what is referred to as herd immunity.

Herd immunity is the term used in both human and veterinary medicine to describe the protection to a group of individuals or animals achieved by protecting (immunizing) a subset of the population. The concept relies on the basis of the percentage of susceptible individuals/animals within a population. As less susceptible individuals/ animals are available for a pathogen to infect, the less likely the pathogen will be able to survive in that population. So even if there are a few susceptible individuals/animals in a group, they can be protected by the surrounding individuals that are protected. Because we do not know which individuals may come in contact with a particular pathogen, our goal is to provide as much herd immunity as possible.

Parasitized/Anemic Animals

One challenging question is whether to vaccinate a less than healthy animal. In an ideal world, we would only vaccinate healthy animals, but unfortunately that is not possible in reality.

Mounting an immune response does require significant energy as well as protein. Anemia by itself (meaning just the lack of red blood cells) should have no significant impact on vaccination response. Vaccination relies primarily on the stimulation of antibodies as well as the stimulation of the cell to mediate immunity response. Red

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blood cells are not part of either of these immune responses. If an animal is anemic due to an infection or due to heavy infestation with internal parasites (which is usually the case), then vaccination will not be as effective. This is because the animal's immune response will already be challenged by these other pathogens but not because of the anemia per se. How parasitized or weak an animal has to be to not respond to a vaccination is not known. The best way to deal with this is to go ahead and vaccinate the animal preferably with a killed product at the same time that they are treated for parasites. A killed product is preferred because MLV vaccines have a modified agent which can be significantly more virulent in a weak or immunocompromized animal. Ideally we would like to come back in two to four weeks and booster the herd allowing for both an anamnestic response (a second more effective immune response) for those already vaccinated as well as possibly getting a first response by those not responding to the first vaccination either due to their previous health condition (i.e. heavy parasitized) or other unknown reasons. Booster vaccinations have tremendous value in increasing the percentage of the population that will be protected and therefore significantly increasing the overall herd immunity that will hopefully protect those that may be weakened enough to not respond to vaccination at all, or at the time of first injection.

Conclusion

I hope this article is able to highlight some important practical points in trying to help you better handle and administer vaccines even under some of the "not so perfect" environments you work in with the objective to maximize animal health for a wholesome and safe food supply for the ever growing human population.

A NOTE ABOUT NEEDLES

Needles come in different lengths and bore sizes (i.e. diameters). On the base of the needle or needle package, the length is indicated in inches or centimeters, and the bore size is indicated as a "gauge." It is usually written like this: " 16G x 1 " This means a 16 gauge needle that is one inch in length.

Length

Most medicines for livestock require a needle 1 to 1.5 inches in length. For subcutaneous injections, 1.0 inch needles are sufficient, although 1.5 inch needles can be used. For deep intramuscular injections, choose 1.5 inch needles if you have them, except in baby livestock where 1 inch needles are sufficient.

Diameter or Bore Size

Most medicines for livestock require 16 to 22 gauge needles; the larger the gauge, the smaller the bore size. The choice of bore size depends on the animal species and size as well as the"viscosity" (thickness) of the medicine.

For baby livestock, 20 or 22 gauge needles are appropriate, unless the thickness of the medicine requires a larger bore. For example, most penicillin cannot be given through a needle smaller than 19 gauge. In adult livestock, 16 to 19 gauge needles are used depending on the thickness of their skin. Large bore (small gauge) needles make it easier to inject medications and don't bend as easy as small bore needles. But more medicine can leak back from a large bore injection site and be wasted.

From "Where There Is No Animal Doctor" by Dr. Peter Quesenberry and Dr. Maureen Birmingham, published by Christian Veterinary Mission. You may buy this book for $15(U.S.) on our website at www.cvmusa.org.

BROKEN NEEDLES

Broken needles in an animal require immediate attention. Veterinarians who have addressed broken needles with ultrasound location and removal tell me needle shafts can mitigate several inches in an hour, either going deeper or moving laterally under the skin or in superficial tissues.

Needle removal is a surgical procedure that's most successful if performed immediately. If the needle can't be identified and removed, the animal should not enter the food chain.

A broken needle is the result of inappropriate needle selection and/or use, likely combined with inappropriate restraint. Injecting cattle in an alley and pasture treatment are two of the most likely situations for broken needles. A bent needle is a broken needle and should be discarded immediately.

When administering drugs in cattle, we have enormous responsibilities to both the cattle and the eventual consumer of our product. Have a plan in place to prevent and respond to drug administration errors.

Adapted from an article written by Mike Apley for Beef Magazine, January 2007, as appeared in AABP Newsletter, February 2007, Pg. 3.

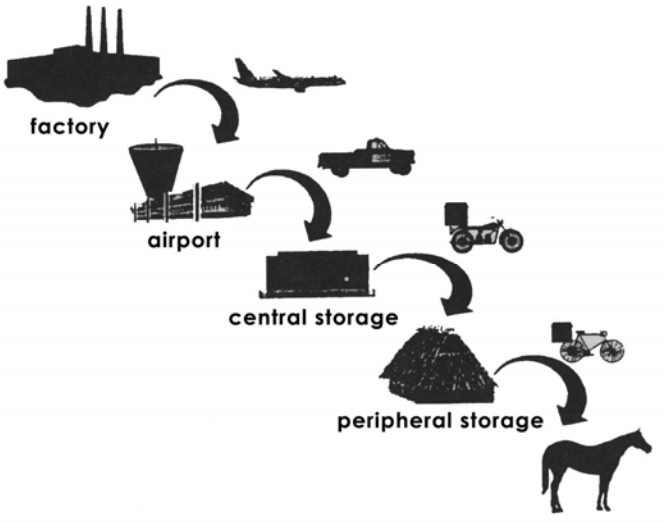
COLD CHAIN

Cold Storage of Vaccines

Most vaccines should be kept at 0 to 8 degrees C. Some vaccines, when stored for longer periods of time (i.e. more than one month), should be frozen. Other vaccines become ineffective if frozen even once. Some vaccines are not sensitive to freezing, but lose their effectiveness if they become warm.

<u>Extremely important:</u> Always read directions! Always follow label instructions on how to store and care for vaccines. The process of keeping the vaccine at the correct temperature from the moment it is manufactured, to the moment it is administered, is called the "**Cold Chain**."

For many vaccines, if the cold chain is broken even once, the vaccine is ruined or at least less effective. There are a few vaccines that don't need refrigeration. These vaccines are called "heat stable" vaccines. For example, a new rinderpest vaccine is heat stable for 30 days.



The Cold Chain

Five Factors That Can Damage Vaccines

1. HEAT

Most vaccines are "heat-sensitive" and must be maintained in a cold chain. They must be stored in a refrigerator at 0 to 8 degrees C, transported in a thermos with ice or cold packs and used immediately once drawn up in a syringe. If the syringe full of vaccine is not used quickly, it should be placed on a cold pack until it's time to inject the vaccine.

2. FREEZING

Vaccines sensitive to freezing will lose their effectiveness if frozen. Many doses of vaccine have been wasted due to accidental freezing. Keep a thermometer INSIDE and check it daily.

3. SUN

Never leave vials or syringes containing vaccine in direct sunlight. When working in the field, open the thermos of vaccine and fill syringes in the shade.

4. CONTAMINATION

Always use sterile needles and syringes when preparing or mixing vaccine or drawing it out of a vial. Never place a used needle in a vaccine vial because this can contaminate the vaccine and cause illness or an abscess at the injection site. **If you suspect that a vial is contaminated, discard it.**

5. DISINFECTANT AND DETERGENT

Disinfectant or detergent may make vaccine ineffective. Therefore, avoid contaminating vaccine with disinfectant or detergent. For example, do not use syringes or needles for vaccination that have residues of disinfectant or detergent left in them form cleaning. Do not use disinfectant when re-sterilizing needles and syringes. For sterilization, rinse thoroughly with <u>water only</u> and then boil in clean water for at least 15 minutes.

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