INVITED COMMENTARY

Rotavirus Serotypes: Classification and Importance in Epidemiology, Immunity, and Vaccine Development

Yasutaka Hoshino and Albert Z. Kapikian

Epidemiology Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA

ABSTRACT

The development and implementation of safe and effective vaccines to prevent the enormous health burden of rotavirus-associated disease is a global public health goal. Human rotaviruses, the major aetiological agents of severe infantile diarrhoea worldwide, display surprisingly diverse and complex serotypic specificities. Ten VP7 serotypes and 7 VP4 serotypes have so far been detected. An increasing number of observations, obtained from analyses of (i) natural rotavirus infections in infants and young children, (ii) experimental rotavirus infections in laboratory animals, and (iii) extensive rotavirus vaccine field trials performed in different populations of various parts of the world, appears to support the concept that serotype-specific antibodies to rotaviruses play an important role in protection against rotavirus-associated illnesses. Thus, the first licensed rotavirus vaccine (RRV-based quadrivalent vaccine) was designed to cover the epidemiologically important VP7 serotype 1, 2, 3, and 4.

Key words: Rotavirus; Serotyping: Epidemiology; Immunity; Vaccine development

INTRODUCTION

Diarrhoeal diseases continue to be a significant cause of morbidity of infants and young children in developing countries. It is also a significant cause of morbidity and mortality in the same age group in developing countries. There is a universal agreement that rotaviruses are the single most important aetiologic agents of severe diarrhoeal illnesses of infants and young children worldwide. Although repeated rotaviral infections occur throughout an individual’s lifetime, symptomatic infections occur most commonly during the first two years of life.

Rotaviruses are estimated to cause over 800,000 deaths annually in children aged less than 5 years in developing countries, and are responsible for over 500,000 visits to a medical practitioner annually in the U.S.A. alone (1,2). Hence, major emphasis has been placed on the development of a safe and effective vaccine for use in early infancy. After over two decades of development, the first rotavirus vaccine (live oral rhesus monkey rotavirus-based quadrivalent vaccine [RotaShield]) was approved by the U.S. Food and Drug Administration for use in a 3-dose regimen in infants at 2, 4, and 6 months of age (1). The success of this live-reassortant vaccine has relied on two major principles: a Jennerian approach by which (i) an animal rotavirus strain (rhesus monkey) confers attenuation, and (ii) outer-capsid proteins induce antibodies to epidemiologically important serotypes. In this invited commentary, we describe the rationale for the importance of defining rotavirus serotypes.

In many viral diseases, neutralizing antibodies appear to play an important role in protection against diseases and/or infections in a type-specific manner. For example, each of the poliovirus serotypes (type 1, 2, and 3) are incorporated in both the live and inactivated poliovirus
vaccines. Similarly, the emergence of novel or unusual serotype(s) of an influenza virus is carefully monitored globally to be ready to detect such a virus, analyze its antigenic composition, and prepare a vaccine carrying appropriate serotype specificities. In this regard, there has been surveillance of rotavirus serotypes in most parts of the world to understand their geographic and temporal distribution to establish the importance of each serotype as a prelude to vaccine development and, in addition, to gain insights into the immune mechanisms of protection. Before delving into the serotypic specificity of rotavirus, we should consider some basic properties of this virus.

**Rotavirus: classification, structure, and antigenic composition**

Rotavirus, which constitutes a genus within the Reoviridae family, is a medium-sized (70 nm) non-enveloped virus. The mature particle consists of a triple-shelled capsid consisting of the outer, intermediate, and inner layers. The outer capsid contains two proteins (VP4 and VP7), whereas the intermediate layer is formed by VP6, and the inner by VP2 which encloses two other proteins VP1 and VP3, as well as the viral genome consisting of 11 segments of double-stranded RNA, the latter encoding six structural and six non-structural proteins (2,2a,3). Because of the segmented nature of the rotavirus genome, genetic reassortment is also determined by VP6, and the inner by VP2 which encloses two other proteins VP1 and VP3, as well as the viral genome consisting of 11 segments of double-stranded RNA, the latter encoding six structural and six non-structural proteins (2,2a,3). Because of the segmented nature of the rotavirus genome, genetic reassortment occurs at high frequency during mixed infection.

Rotaviruses carry three important antigenic specificities: group, subgroup, and serotype. Based on group specificity which is conferred predominantly by VP6, rotaviruses are divided into 7 groups (A to G). Human rotavirus (HRV)-associated infections are predominantly caused by group A, and less commonly by group B or C, and thus, the emphasis of vaccine development has been targeted at group A rotavirus-associated disease. Of note is the finding that group B rotavirus (adult diarrhoea rotavirus [ADRV]) which caused large outbreaks in China in the 1980s was recently (1997 and 1998) detected in patients with diarrhoea in India, marking the first emergence of group B ADRV outside China (4). Subgroup specificity, which is also determined by VP6, has been used for characterizing the antigenic properties of various rotavirus strains in epidemiologic surveys. Most HRVs belong to either subgroup I or subgroup II. Central to our discussion are the outer-capsid proteins VP4 and VP7 which specify rotavirus serotype specificities independently; VP4 is a spike protein, whereas VP7, a glycoprotein, is more abundant, and constitutes the major portion of the outer surface (2,3,5).

**Rotavirus VP4 and VP7 serotypes**

Analyses of monoclonal antibodies (mAbs) directed against rotavirus outer-capsid proteins VP7 and VP4 (6) of naturally-occurring or laboratory-generated rotavirus reassortants (7,8) have shown that both VP7 and VP4 carry epitopes that are responsible for evoking neutralizing antibodies. Later, the independent protective immune properties of the VP7 and VP4 were also defined (9-12). Thus, a binary system of rotavirus classification to designate the neutralization specificity of both VP7 and VP4 outer-capsid proteins was established, similar in concept to the dual system used for the influenza A viruses (13). The VP7 serotype is designated as G (because VP7 is a glycoprotein) serotype, whereas the VP4 serotype is designated as P (because VP4 is protease-sensitive) serotype. Neutralizing antibodies in hyperimmune antiserum raised against a rotavirus strain are primarily directed to the major surface glycoprotein VP7. However, hyperimmune antiserum raised against reassortant rotaviruses, in general, demonstrates high-neutralizing activities not only to the VP7 but also to the surface spike protein VP4 (14). This difference may be due to conformational factors (15).

In neutralization assays with hyperimmune antisera and the criterion of a greater than 20-fold difference between homologous and heterologous reciprocal neutralizing antibody titres, it has been possible to designate 14 rotavirus G serotypes and 11 rotavirus P serotypes (2,3,16,17). Most serotypes are shared between humans and animals; 10 of the 14 G serotypes (G1, 2, 3, 4, 5, 6, 8, 9, 10, and 12) and 7 of the P serotypes (P1, 2A, 3, 4, 5A, 8, and 11) have been detected in humans. Only G serotype 7, 11, 13, and 14 and P serotype 6, 7, 9, and 10 have been detected exclusively in animals. The neutralization assay is by definition the only method of determining neutralization specificity (serotype) of VP7 or VP4. The assay requires type-specific high-titre polyclonal hyperimmune antisera and, in addition, is time-consuming and labour-intensive. Hence, to circumvent the lack of appropriate and readily-available reagents for serotyping according to VP7 specificity and to enable the typing of a large number of rotavirus field isolates, a proxy method was developed employing a type-specific mAb-based ELISA.

Four sets of independently-developed VP7-specific mAbs have so far been used extensively in epidemiologic surveys (18,19,20,21), and 2 sets of typing ELISA kits are available commercially. These VP7-specific mAbs are either neutralizing or non-neutralizing, and provide a method for typing the epidemiologically most important HRV G serotype 1, 2, 3, and 4. Since antigenic drift due to accumulation of point mutations on the VP7 protein appears to occur in nature (22), the use of multiple combinations of selected mAbs is necessary to maximize the typing efficiency of rotavirus field isolates (23,24). In addition, mAbs have been generated to identify HRV G serotypes other than 1 to 4 (i.e. G5, 6, 8, 9, 10, and 12) (5). Furthermore, “type-specific” mAbs, designed to type epidemiologically important HRV P serotype 1A, 1B, and
Rotavirus VP7 and VP4 genotypes

Other popular proxy VP7 and VP4 typing methods include type-specific cDNA probe-based hybridization (31,32) and type-specific primer-based RT-PCR (33-35). These methods are designed to type the gene group (allele) of the individual VP7 gene (G genotype) or VP4 gene (P genotype) of a rotavirus. Such assays have been widely used for genotyping rotavirus field isolates, and complete concordance between VP7 genotype and VP4 genotype has so far been observed.

Since the VP7 gene (and possibly also the VP4 gene) carries species-specific sequences (36), caution must be exercised when “type-specific” probes or primers which are designed to genotype rotaviruses derived from humans or animals are used. In addition, as point mutation(s) on the VP4 or VP7 protein affect(s) the reactivities of mAbs employed in the typing ELISA, point mutation(s) on VP4 or VP7 gene can also influence the “type-specificity” of primers used in genotyping RT-PCR. Thus, a second set of “type-specific” primers is advisable for genotyping “non-genotypeable” rotavirus specimens by the first set of primers or for confirmation of genotype-questionable rotavirus isolates.

The formal numerical designations for G serotypes and G genotypes have been identical, and, thus, only a single number is used (e.g. G1). However, in contrast, the numbers assigned for P serotypes and P genotypes are different, causing considerable confusion. To clarify this situation, a P serotype is now designated as P followed by the assigned number in brackets, e.g. P1A[8] (3).

Rotavirus serotypes/genotypes and rotavirus epidemiology

G serotyping and G and P genotyping assays described above have been used extensively for typing HRV field isolates in various epidemiologic surveys (33, 37-60). Such studies have generated important information, such as: (i) G serotype 1, 2, 3, and 4 constitute more than 90% of all G serotypes detected worldwide; (ii) G serotype 1, 3, and 4 are most commonly associated with P type 1A[8], whereas G serotype 2 segregates preferentially with P type 1B[4]; (iii) various other HRV G serotypes, such as G5, 6, 8, 9, 10, and 12 with P types, such as P2A[6], 3[9], 4[10], 5A[3], and 11[14], have been detected in various locations, but their prevalence has for the most part remained localized; (iv) multiple G and P types can cocirculate within the same region; (v) the prevalence of rotavirus serotypes in different regions within the same country can differ during the same year; (vi) the prevalence of individual serotypes in the same region can show a yearly change; and (vii) no correlation between disease severity and rotavirus serotypes has been demonstrated.

Unusual G and P serotypes, associated with asymptomatic or symptomatic infections, have more recently been reported from various parts of the world. For example, asymptomatic rotavirus infection was detected among infants in paediatric wards of 6 hospitals and clinics in Bangalore, India (61). Later, this infection was shown to be caused by a rotavirus strain which had an antigenic composition of G10,P8[11], a G-P combination commonly found in cattle (62). Similarly, in New Delhi, India, another rotavirus strain carrying G9,P8[11] specificity was reported to cause asymptomatic neonatal infection which persisted in the maternity unit for more than one year (33). By RNA-RNA hybridization, these Indian neonatal rotavirus strains appeared to be reassortants between human and bovine rotaviruses (63,64).

The G and P genotypes of 63 rotavirus isolates derived from children with diarrhoea, collected between April and December 1993 from 5 Indian cities, were determined (65). The common G1, 2, 3, and 4 genotypes accounted for 54%, followed by G9 (24%), mixed G genotypes (11%), and non-typeable G genotypes (11%). Forty-three percent of these isolates belonged to P[6] genotype, followed by P[4] (21%), P[8] (13%), P[11] (1%), mixed P genotypes (11%), and non-typeable P genotypes (11%).

In 1994, the presence of a G5 rotavirus strain, which is the most common G serotype found in pigs, was detected in infants and young children in Brazil (66). In that study, of 139 rotavirus isolates, derived from diarrhoeic children, and which were collected between 1986 and 1992 in São Paulo, Brazil, it was found that 50% of them were the common G1, 2, 3, and 4 genotypes, 17% G5 genotype, 12% mixed G genotypes, and 21% non-typeable G genotypes (56,66). Forty percent of these rotavirus strains belonged to genotype P[8], P[4], or P[6], followed by P[3] (11%), mixed P genotypes (29%), and non-typeable P genotypes (20%). Later, RNA-RNA hybridization assay suggested that the most frequently detected genotype G5P[8] was a possible human-porcine rotavirus reassortant (67).

The G and P types of 348 rotavirus isolates, obtained during 1996-1997 from children with diarrhoea in 10 U.S. cities, were determined (51). Eighty-three percent of them were the common G1P[8], G2P[4], G3P[8], and G4P[8]. Of note is the finding that rotavirus strains carrying unusual G9 (7.2%) or P[6] (6.9%) specificities were detected.

2A have also been developed and used in typing ELISA but in only a limited fashion (25-30) However, typing specificities of such VP4-specific mAbs are not as clear-cut as VP7-specific mAbs, and further refinement of such typing ELISAs may be necessary.

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More recently, 100 rotavirus isolates, detected from children with diarrhea in Blantyre, Malawi, during 1997-1998, were characterized for G and P types by RT-PCR (41). The G8 genotype was found to be a predominant strain (51%), and the P[6] genotype was identified in 57% of the strains overall. The distribution of such HRVs carrying unusual or novel G and/or P types has so far been focal. In spite of the variance of P genotypes among strains, the predominant G serotypes circulating worldwide have G1, 2, 3, or 4 specificity. The recently-licensed rotavirus vaccine is aimed at protecting against these G serotypes. However, continued surveillance for temporal and geographic trends of rotavirus infections should continue, particularly because of the licensure of the first rotavirus vaccine in the United States to understand the natural history of serotype distribution. It is of note that the rotavirus isolates carrying unusual G types (G5, 8, 9, or 10) were all detected first by RT-PCR, because such serotypes are not detectable by commercially available serotyping ELISA kits which contain mAbs specific only for G1 to G4.

**Rotavirus serotypes and rotavirus immunity**

Analysis of reactivities of neutralizing mAbs raised against rotavirus VP7 or VP4 has revealed that both VP7 and VP4 proteins carry serotype-specific and serotype-cross-reactive epitopes (5). Such reactivity has also been found in hyperimmune antiserum made in guinea pigs, in which the highest level of neutralizing activity is to the homologous virus with lower or undetectable levels of neutralizing activity to certain heterologous viruses (68). This is particularly relevant, because guinea pigs have never been known to undergo natural rotavirus infection. In addition, infection sera of gnotobiotic animals possess both high homotypic and lower heterotypic neutralizing activities (69,70). Furthermore, neutralizing antibody responses of gnotobiotic animals exposed to oral or parenteral rotavirus vaccine (bovine rotavirus UK strain) were highest to VP4 and VP7 of the homologous immunizing virus, next highest to viruses which were related via VP4 or VP7 to that of the vaccine virus, and lowest to viruses which were not related via VP4 or VP7 to that of the infecting virus (70). In primary infections in gnotobiotic animals, significant serum antibody responses to VP4 or VP7 were approximately equal as determined by neutralization assay and epitope-blocking assay (70).

Serologic responses to rotavirus neutralization epitopes of immunologically-naive animals, e.g., gnotobiotic animals, are much narrower than those of immunologically-experienced animals, e.g., adult animals, that have presumably been infected multiple times with rotavirus (70). Similarly, infant vaccinees develop predominantly homotypic responses to vaccine virus, whereas adult vaccinees produce antibodies to homotypic and a wide range of heterotypic rotaviruses (71). This phenomenon has been documented in immunologically-naive gnotobiotic animals which, following exposure to multiple cycles of infection with one rotavirus serotype, develop antibodies that neutralize a broad range of rotavirus serotypes (72).

In animal models, both after active and passive immunization, serotype specificity of a rotavirus appears to play an important role in protection against disease and/or reinfection caused by a virulent challenge virus. This has been demonstrated both in large (e.g. calf, lamb, and piglet) (73-77) and small (e.g. mouse) (78) animals. In many of these studies and in studies in which neutralizing antibodies did not appear to play an important role in protection against disease or infection (79-81), the neutralization specificities on VP4 and/or VP7 of the immunizing or the challenge virus were not well characterized. Therefore, caution must be exercised in interpreting studies wherein both VP4 and VP7 were not defined.

The importance of either VP4 or VP7 was shown in a porcine animal model challenge study in which two porcine rotavirus G4P2B[6] and G5P9[7] exhibited no cross-protection in gnotobiotic piglets (82). However, using a homologous system of gnotobiotic piglets and G4P2B[6], G5P9[7] porcine rotaviruses, and a reassortant G4P9[7], we found that an initial single enteric infection conferred protection to piglets three weeks later against disease and reinfection caused by the virulent challenge virus only when either VP4 or VP7 serotype of the challenge virus was shared with the initial immunizing virus (9). In addition, cross-protection studies in animals (78,83) and observations made in children (84-88) demonstrated that not only type specificity of anti-VP4 and anti-VP7 antibodies but also the level of titres of antibodies were important in protection against disease.

Several cohort studies have been performed to assess the protective efficacy of a natural rotavirus infection against subsequent reinfection and disease. The first of such studies which included a follow-up of 2 groups of infants for 3 years—one with neonatal asymptomatic rotavirus infection and one without neonatal rotavirus infection—showed that although the rotavirus infection rates were almost identical, the occurrence of rotavirus illnesses was less frequent and less severe in those with prior neonatal infection than in those without such neonatal infection (89). Neonatal rotavirus infection conferred protection against subsequent severe symptomatic disease, but did not prevent reinfection. The mechanism underlying such immunity has not yet been established, although neutralizing antibodies may play an important role.

Faecal, serum, and salivary anti-rotavirus antibodies (IgM, IgA, IgG, neutralizing and epitope-blocking) have been used as surrogate markers in cohort studies to
identify immunologic correlates of protection. The findings of one of the most extensively-analyzed cohort studies, carried out in Mexico (88,90,91), indicated that (i) first infections generally are the most severe, with severity decreasing as the number of infections increases; (ii) protection conferred by infection exhibits a gradient of efficacy against subsequent outcomes, being greatest against moderate-to-severe illness, lesser against mild illness, and least against asymptomatic infection; (iii) asymptomatic infection confers protection to a degree comparable to that achieved by symptomatic infection; (iv) complete protection against moderate-to-severe infection results from the accumulated experience of two infections, regardless of whether the infections are symptomatic or asymptomatic; (v) higher serum antibody titres of anti-rotavirus IgA, IgG, or homotypic G type-specific blocking antibody are associated with protection against infection and illness; and (vi) repeated infections with the same G serotype are less likely to occur, suggesting homotypic protection.

Recently, selected anti-VP6 non-neutralizing IgA mAbs secreted from “backpack tumor” transplants were shown to protect adult mice from primary and resolving chronic murine rotavirus infections presumably via intracellular viral inactivation during transcytosis (92). Later, with the same system, selected anti-VP8 (trypsin mAbs secreted from "backpack tumor" transplants were shown to protect adult mice from primary and resolving chronic murine rotavirus infections presumably via intracellular viral inactivation during transcytosis (92). Such antibodies and antibodies directed to serotype-cross-reactive neutralization epitopes on VP7 and VP4, and serotype-cross-reactive rotavirus-specific cytotoxic T lymphocytes directed to VP7 (94-96), may be of importance in heterotypic protection.

**Rotavirus serotypes and rotavirus vaccine development**

Rotavirus vaccines, given orally to humans, comprised live-attenuated strains. In this approach, a live-oral vaccine mimics a natural rotavirus infection and, thus, protects against clinically significant disease after subsequent infection. Monovalent bovine (NCDV RIT4237 G6P6[1] and WC3 G6P7[5]) and simian (rhesus rotavirus [RRV] strain MMU18006 G3P5B[3]) rotavirus vaccines were developed based on a Jennerian approach (97-99), and were evaluated extensively. These vaccines, shown to be safe and immunogenic, could not consistently induce substantial heterotypic protection after vaccination. Because of this, a modified Jennerian approach was pursued. In this strategy, an animal rotavirus is used as a donor of attenuation phenotype for generating reassortant vaccine candidates that derive 10 genes from the animal rotavirus and one gene from the human rotavirus strain, the latter encoding the neutralization protein VP7 of one of the epidemiologically important HRV G serotypes (100,101).

The recently-licensed rhesus rotavirus-based vaccine (RotaShield) consists of RRV (G3P5B[3]) and 3 RRV-HRV reassortant rotaviruses. Each reassortant derives 10 genes from RRV and a single HRV gene encoding G serotype 1, 2, or 4 specificity (G1P5B[3], G2P5B[3], and G4P5B[3]). This vaccine, extensively evaluated in different populations in various parts of the world, has been shown to be safe, immunogenic, and highly effective against severe dehydrating rotavirus-associated diarrhoea (101-103). In addition, in a recent multicentre efficacy trial carried out in 23 centres in the United States (104), both RRV-based quadrivalent vaccine and a RRV-HRV G1 monovalent vaccine provided comparable protection against the most frequently-detected G1 serotype in the first year. However, in the second year when non-serotype G1 rotavirus infections accounted for about one-third of rotavirus-associated disease, the quadrivalent vaccine provided significant protection when compared to the monovalent vaccine (p<.03) and tended to protect when compared to the placebo (p=.07), suggesting a lack of heterotypic protection by the monovalent G1 vaccine. Moreover, in a later multicentre study in which the quadrivalent and monovalent (G1) RRV-based vaccines were evaluated at a 10-fold higher dose for each serotype, the vaccines provided comparable protection against the predominant G1 serotype (105). However, the quadrivalent vaccine but not the monovalent vaccine provided significant protection against illnesses associated with the second most common G3 serotype (19%), when compared with the placebo (p<.01). The quadrivalent vaccine only tended to protect against G3 serotype illnesses when compared with the monovalent vaccine (77% vs 45%) (p=.14) (105). Similarly, in the trial performed in a native American population in Arizona and New Mexico (106), efficacy against any rotavirus diarrhoea caused by the prevailing G3 rotavirus, provided by the quadrivalent vaccine, was significantly greater (53%) than that provided by the RRV-G1 monovalent vaccine (20%). This suggests that the modified Jennerian approach by which the VP7 of each of the 4 epidemiologically important serotypes were incorporated into a single vaccine was important to achieve broad protection. The quadrivalent vaccine also tended to induce a higher level of protection against severe G3 rotavirus-associated diarrhoea when compared with the monovalent G1 vaccine (69% vs 48%).

Other currently-available vaccine candidates which have been at least in phase-I human trials include the following: (i) bovine rotavirus UK-based quadrivalent vaccine (G1P7[5], G2P7[5], G3P7[5], and G4P7[5]) (107,108); (ii) bovine rotavirus WC3-based quadrivalent vaccine (G1P7[5], G2P7[5], G3P7[5], and G6P1A[8]) (100); (iii) vaccines carrying HRV VP4 (P1A[8]) in the gene background of the UK which can be added to the existing UK-based quadrivalent vaccine to formulate a pentavalent vaccine; (iv) double-gene substitution reassortant vaccine which derives HRV P serotype 1A[8],
G serotype 2, and the remaining 9 UK genes (109); (v) cold-adapted HRV vaccine D(G1P1A[8]), (110); (vi) a HRV candidate vaccine 89-12 (G1P8) attenuated by 33 passages in monkey kidney cells (111); (vii) a HRV candidate vaccine RV3 (G3P[6]) derived from an asymptomatic neonate (112) and; (viii) a lamb rotavirus candidate vaccine LLR (G10P[12]) (112). Although precise protective mechanisms in vivo of antibodies directed to VP4 and VP7 are still not known, since neutralization mechanisms in vitro of selected anti-VP4 and anti-VP7 antibodies have been shown to be different (113), such vaccines incorporating both HRV VP4 and VP7 components may possibly be more effective in protection against disease than vaccines carrying either HRV VP7 or VP4 component alone. Furthermore, since G5, G8, Kp19 and G10 HRVs have been detected in different populations, albeit focally, incorporation of such strains into existing vaccines may be necessary, if warranted from epidemiologic evidence.

CONCLUSION

Whether rotavirus serotype-specific neutralizing antibodies (immunity) play an important role in protection of neonates, infants, and young children against rotavirus-associated diarrhoea is still under discussion. However, as presented in this review, evidence supporting the important role of serotype-specific immunity appears to be increasing. Contributing to this point of view has been the evidence garnered from recently-completed field trials in infants and young children with the newly-licensed thressus rotavirus-based vaccine which suggests that immunity to specific serotypes is important. Bachmann and Zinkernagel in a viewpoint commentary observed that “Viruses that are controlled efficiently by antibodies often form serotypes (114). If this observation is extrapolatable to this point of view has been the evidence garnered from epidemiologic evidence.

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