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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ANA WHITLOW, et al.,

Plaintiffs,

vs.

STATE OF CALIFORNIA, et al.,

Defendants.

Case No. 3:16-cv-01715-DMS-BGS

PLAINTIFFS' REPLY TO STATE DEFENDANTS' OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION

Courtroom: 13A
Judge: The Honorable Dana Makato Sabraw
Trial Date: None Set
Action Filed: July 1, 2016

Hearing Date: August 12, 2016
Hearing Time: 1:30 p.m.

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INTRODUCTION

The 2016-17 school year is different from prior years – and not in a good way. This year, more than 33,000 California children, many with learning disabilities and special needs, are permanently barred from all public and private schools and daycares. These children have a fundamental right to a classroom-based education and they want to go to school. Yet in a dramatic departure from its history of unwavering protection of every child's right to an education, and without satisfying strict scrutiny, California has enacted Senate Bill ("SB") 277 to abolish the Personal Belief Exemption ("PBE") to its mandatory vaccination law and to permanently bar children with PBEs from school. But the U.S. and California Constitutions, as well as an array of federal and state disability and anti-discrimination laws, prohibit SB 277's draconian result and necessitate injunctive relief.

Plaintiffs' Motion for Preliminary Injunction exceeds the showing required for injunctive relief to maintain the *status quo ante* pending the outcome of this case. Plaintiffs provide a detailed analysis of the facts and law to demonstrate likelihood of success on the merits of their claims for deprivation of the right to education under the California Constitution, deprivation of free exercise, equal protection and due process rights under the U.S. Constitution, which protects parental rights, bodily integrity and informed consent, and violation of both State and Federal disability and anti-discrimination rights. Plaintiffs provide extensive evidence of irreparable injury, establish that the balance of hardships tips overwhelmingly toward Plaintiffs, and demonstrate that an injunction will serve the public interest. Plaintiffs also demonstrate that the *status quo ante* properly protects Plaintiffs' rights and the public health by allowing temporary exclusion of children with PBEs in the event of an outbreak or exposure to an illness for which they have not received a vaccine.

In response, State Defendants attempt to confuse the issues and mislead the Court as to the facts and the law, without addressing Plaintiffs' arguments and evidence. While conceding that SB 277 deprives Plaintiffs and their children of

fundamental rights, State Defendants contend, in a surprisingly cavalier tone, that the deprivation of those rights is justified. They unapologetically admit, for example, that SB 277 denies Plaintiffs' children education based on nothing more than the unfortunate misperception of those children – who are neither infectious nor contagious – as carriers of "dangerous diseases" and "threats to public health," Opp., Doc. 30, at 9. State Defendants base their arguments on biased, unsupported, and inadmissible statements from SB 277's author and sponsors contained in legislative committee reports and on conclusory testimony from a declarant who, without laying a proper foundation for his opinions, contradicts Defendants' own data and reports.[1]

Defendants also misrepresent SB 277's purpose and effect in a strained and irrelevant analysis that attempts to turn this case on its head and shift the focus from Plaintiffs' actual claims to issues that Defendants would prefer to litigate. Defendants base their entire Opposition on the argument that the State has the authority to enact vaccine mandates. But Defendants ignore the fact that SB 277 did not enact a vaccine mandate. California's vaccine mandates, codified in Health and Safety Code sections 120325(a)(1) - (10) and 120335(a)(1) - (10), predate SB 277 and were unchanged by it. Instead, SB 277 repealed Health and Safety Code section 120365 and abolished PBEs, subject to an arbitrary "checkpoint" scheme that serves no public health benefit. Accordingly, the cases on which Defendants rely to support SB 277 are irrelevant and easily distinguishable on the foregoing and other grounds.

Plaintiffs seek to enjoin SB 277's enforcement to allow kindergarten and seventh grade children with PBEs to return to their schools and obtain the education to which they are constitutionally entitled, pending the outcome of this case.

[1] As set forth in Plaintiffs' Evidentiary Objections, legislative committee reports are inadmissible. They lack foundation, include opinions from various named and unnamed supporters and opponents of a bill, contain hearsay, and contradict publicly-available California Department of Public Health ("CDPH") and Centers for Disease Control and Prevention ("CDC") data and reports that Plaintiffs have asked the Court to judicially notice. Similarly, most of Robert Schechter, M.D.'s declarations is inadmissible for lack of foundation and hearsay, leaving Defendants' Opposition with virtually no factual support.

Plaintiffs' request is modest and consistent with 55 years of pre-SB 277 law. Defendants, on the other hand, ask this Court to allow the unprecedented denial of education to tens of thousands of children who face loss of protected education and special education rights, possible truancy, and removal from their families and whose parents face severe hardship including loss of employment or loss of parental custody. Without injunctive relief, this year alone, approximately 13,000 children will not experience their first day of kindergarten and more than 8,000 pre-teens/teenagers will not advance to the seventh grade. These children make up less than half of one percent of the State's school population and cannot impact public health. Yet the harm to each child from being denied an education is immense and irreparable.

Plaintiffs respectfully request that the Court grant their Motion and preserve the *status quo ante* while the parties litigate this case. California's children deserve better than to be barred from school and subjected to forced permanent quarantine, isolation, humiliation, prejudice, and emotional distress because of an unnecessary, draconian and discriminatory law that flies in the face of the State's compelling interest in educating children. *See Serrano v. Priest*, 5 Cal.3d 584, 605 (1971) ("[E]ducation is a major determinant of an individual's chances of economic and social success…a unique influence on a child's development as a citizen and his participation in political and community life. … Thus, education is the lifeline of both the individual and society.")

STATEMENT OF FACTS

I. DEFENDANTS IGNORE AND MISREPRESENT THEIR OWN DATA

Motivated by special-interest politics, SB 277 is an unnecessary solution to a non-existent problem, introduced when California's children were, according to CDPH, "well protected" from communicable diseases. Defendants claim "SB 277 was a reasoned response to escalating numbers of unvaccinated children and further outbreaks of dangerous communicable diseases." Opp., Doc. 30, at 18. But California did not have "escalating numbers of unvaccinated children" when SB 277 was

introduced. As CDPH reports show, prior to SB 277's introduction and enactment, kindergarten PBE rates had dropped 19%, from an already low 3.15% in 2013-14 to 2.54% in 2014-15. Rates fell another 7% in 2015-16, to 2.38%. CDPH 2015-16 K Assess., RJN, Doc. 13-5, Ex. 2. In fact, at SB 277's introduction, California's vaccination rate was "at or near all-time high levels" Motion, Doc. 14-1, at 16.

Defendants' claim that only 92.9% of kindergarten children in 2015-16 had all required vaccines improperly lumps conditional entrants with PBE students. Conditional entrants - typically 5-7% of kindergarteners – are not exempt and must become fully-vaccinated within the time specified by the school district. Motion, Doc. 14-1, at 19-20. California's PBE rate has never exceeded 3.2%, *id.* at 5, and was only 2.54% when SB 277 was introduced. Defendants provide no evidence to the contrary except to attempt to artificially inflate the percentage of children with PBEs.

II. DEFENDANTS TREAT HEALTHY CHILDREN AS "DISEASE CARRIERS"

Defendants characterize Plaintiffs' children – all of whom are selectively vaccinated, none of whom carry any illnesses, and some of whom have laboratory-confirmed immunity – as "unvaccinated" carriers of "potentially fatal diseases." Opp., Doc. 30, at 4, 9. Defendants do not explain how Plaintiffs' healthy children are a "danger to public health" or how their exclusion from school "protects the public." Defendants also provide no justification for forcing children with lab-confirmed immunity take another vaccine to attend school, subjecting them to the risk of an unnecessary medical procedure. *See* Whitlow Dec., Doc. 13-2, ¶¶ 18-19. Defendants also ignore that some children become immune with fewer vaccine doses, while others never acquire immunity no matter how many doses they take. Indeed, the State simply assumes every fully vaccinated child is "immunized" and every child who has not received every single one of the 30 to 38 required doses as an "unvaccinated public health threat" even where the child has lab-confirmed immunity.

Moreover, most children with PBEs are vaccinated. They have simply not received every single dose California mandates. *See* Motion, Doc. 14-1, at 7, n3. Indeed, only 0.316% of California children are completely vaccine-free and they are not "public health threats" either. *Id.* Thus, Defendants' characterization of every child with a PBE as "unvaccinated" and diseased is disingenuous, to say the least.

Finally, according to CDPH, Californians are well-protected without SB 277. For 2014, with the exception of pertussis,[2] there were few – and in many instances no — cases reported of the ten diseases for which California mandates vaccines and no outbreaks were attributable to children with PBEs. *See* CDPH, 2014 Annual Report, RJN, Doc. 13-3, Ex. 23, at 8, 13-15, 17-19, 23-37. Therefore, there is no basis to permanently exclude any child from school.

III. DEFENDANTS MISREPRESENT THE PRESENCE OF FETAL TISSUE IN VACCINES AND THE CATHOLIC CHURCH'S POSITION

Defendants distort facts in their attempt to dismiss Plaintiffs' sincerely held religious beliefs against the use of cell lines derived from aborted fetal tissue in vaccine manufacture, even though this belief has served as the basis for religious exemptions. *See* NYS Ed. Dept. Dec. 16,805 (Aug. 3, 2015), Reply RJN Ex. 1. The use of cell lines derived from aborted fetal tissue in vaccines is indisputable. *See* CDC Vaccine Excipient Table, Reply RJN Ex. 2; manufacturer product inserts, Reply RJN Ex. 3. The Catholic Church, as described in Pontifical Academy for Life's statement "Moral Reflections on Vaccines Prepared from Cells Derived from Aborted Human Fetuses" strongly condemns the use of aborted fetal tissue in vaccine manufacture and recognizes that families "should take recourse, if necessary, to the use of conscientious objection with regard to the use of vaccines produced by means of cell lines of aborted human fetal origin." Reply RJN Ex. 4, at 6-7.

[2] Pertussis outbreaks occur mostly in vaccinated children and result from vaccine failure and waning immunity, not PBEs. *See* Motion, Doc. 14-1, at 7.

IV. MEASLES OUTBREAKS DO NOT JUSTIFY SB 277

Predictably, the State continues to rely on the Disneyland measles outbreak to justify SB 277 by reciting that 18 children were not vaccinated. Opp., Doc. 30, at 7. The State does not dispute that no evidence shows that children with PBEs caused or exacerbated the outbreak or that kicking children out of schools will prevent measles outbreaks at theme parks. The State also refers to a 2008 measles outbreak in San Diego to justify SB 277. Opp., Doc. 30, at 7. What the State ignores is that both outbreaks began with foreign-imported measles and ended with relatively few people affected. Despite originating from a foreign visitor in one of the most populous places in the state, where more than 60,000 people were potentially exposed, the Disneyland outbreak affected a total of 136 Californians and was quickly contained. Defendants present no evidence that Disneyland, or any outbreak, would have been any different if children with PBEs had been permanently barred from school. Moreover, if anything, the Disneyland outbreak shows that even when many thousands are exposed to measles, very few become infected, belying Dr. Schechter's speculation that California is on the verge of a pandemic so imminent that draconian actions, like repealing PBEs or permanently isolating healthy schoolchildren is necessary.

Importantly, Defendants do not even attempt to justify the repeal of PBEs for the nine other vaccines California mandates. No justification exists with California's 97% vaccination rate which Defendants concede is sufficient to satisfy the theory of "herd immunity." Moreover, tetanus is non-communicable, hepatitis B is blood-borne, the mumps vaccine is highly ineffective and virtually every person affected in mumps outbreaks is fully vaccinated, the pertussis vaccine does not prevent infection or transmission and wanes quickly, chickenpox is a mild childhood illness, and diphtheria, polio and rubella are essentially eliminated in the United States and do not circulate in California schools. *See, e.g.*, CDPH, 2014 Annual Report, RJN, Doc. 13-6, Ex. 23, at 5, 13, 30, 33; Pertussis Report, RJN, Doc. 13-5, Ex. 6; Examples of outbreaks in highly vaccinated populations, Reply RJN Ex. 5.

V. SB 277 CANNOT ELIMINATE OUTBREAKS

Defendants claim SB 277 is necessary to make California schools "disease-free." But if SB 277's "end" is to prevent outbreaks, then the "means" of excluding children from school cannot justify that unattainable "end." SB 277 will not actually increase overall vaccination rates – it will only artificially inflate school vaccination rates by excluding children with PBEs. These children will remain in the community and will participate in sports, go to stores and theme parks, and have playdates. But they will be permanently barred from the most important place – school. SB 277 also cannot prevent outbreaks because, as evidenced in countless published case reports and news articles, outbreaks of "vaccine-preventable" illnesses like measles, whooping cough, and mumps regularly occur in highly vaccinated communities. *See, e.g.*, Reply RJN Ex. 5.

VI. SB 277'S IMPLEMENTATION HAS CREATED TURMOIL AND CONFUSION FOR SCHOOLS AND FAMILIES

By their own actions and inactions, CDPH and the Department of Education ("CDE") have created confusion for parents, schools, local public health agencies, and medical practitioners. CDE refuses to provide guidance to school districts regarding admission of children with IEPs, leaving children with disabilities at the mercy of local school districts even though federal law requires the State to provide each of these children a Free and Appropriate Public Education ("FAPE"). Defendants concede that "[t]he IDEA provides that a state must, in order to receive federal financial assistance, have policies and procedures in effect that assure all students with disabilities the right to [FAPE]" and that "CDE has general oversight responsibility for special education in California." Opp. Doc. 30, at 26, 28. Yet CDE attempts to absolve itself of any responsibility to supervise local school districts, telling Plaintiffs and tens of thousands of other parents to take their grievances up with their local school districts. This is an unlawful abdication of CDE's duties and CDE appears unconcerned that at issue are the rights of thousands of federally-

protected children with disabilities who are not receiving services they need, causing them tremendous hardship and detriment. CDE's position is an admission that, with the State's knowledge and consent, school districts are violating the equal protection rights of children with IEPs who are being treated differently across the state depending upon the district in which they reside and attend school. This fact alone is sufficient to warrant injunctive relief.

CDPH has created even more confusion, as the Health and Safety sections of the California Code of Regulations ("CCRs") still recognize PBEs and require schools to unconditionally admit students with PBEs into school. *See* 17 Cal. Code Reg. § 6051 ("[a] pupil with a permanent medical exemption or a personal beliefs exemption to immunization shall be admitted unconditionally."); 17 Cal. Code Reg. § 6075 (setting reporting requirements on the number of students with PBEs); 17 CCR § 6055 (concerning students who are not vaccinated and do not have a PBE or medical exemption). The CDPH website also advises that PBEs are available. *See, e.g.*, https://www.cdph.ca.gov/HEALTHINFO/DISCOND/Pages/Measles.aspx, Reply RJN Ex. 6 ("Some children are allowed by California law to skip immunizations if a parent submits a personal beliefs exemption (PBE) or medical exemption (PME) at enrollment"). Thus, while taking the position that PBEs are no longer available, CDPH expressly makes PBEs available under the CCRs, which "have the effect of law." *See* http://www.oal.ca.gov/ccr.htm, Reply RJN Ex. 7. Accordingly, under the current statutory framework, PBEs are available, even though, at CDPH direction, schools refuse to admit children with PBEs into school. Notwithstanding the above, CDPH claims that everything should have been clear to parents when CDPH itself is violating its own CCRs. CDPH's inability to consistently interpret SB 277 and failure to provide consistent guidance to parents and schools continues to today. *See*, *e.g.*, July 2, 2015 letter from CDPH, Reply RJN Ex. 8 (declaring SB 277 effective July 2016); February 4, 2016 Bd. of Directors Mtg., Cal. Conf. of Local Health Officers, Reply RJN Ex. 9 (CDPH unsure on certain issues of SB 277 implementation);

February 4, 2016 SB 277 – Update, Reply RJN Ex. 10, at 5 ("CDPH continues to review SB 277 in consultation with CDE and CDSS"). Accordingly, any argument that the law is clear and Plaintiffs have had months to prepare for it lacks any merit.

ARGUMENT

Defendants concede that SB 277 deprives Plaintiffs of their fundamental rights, including the fundamental right to education under the California Constitution. To protect those rights, Plaintiffs ask this Court to enjoin enforcement of SB 277 and maintain the *status quo ante* during the pendency of this case. A preliminary injunction "is not a preliminary adjudication on the merits but rather a device for preserving the status quo and preventing the irreparable loss of rights before judgment." *U.S. Philips Corp. v. KBC Bank N.V.*, 590 F.3d 1091, 1094 (9th Cir. 2010). Its purpose "is merely to preserve the relative positions of the parties until a trial on the merits can be held." *Univ. of Texas v. Camenisch*, 451 U.S. 390, 395 (1981). To obtain a preliminary injunction, a showing that there is a "reasonable probability of success – not an overwhelming likelihood – is all" that is needed. *Gilder v. PGA Tour, Inc.* 936 F.2d 417, 422 (9th Cir. 1991). When a violation of constitutionally protected rights is shown, no further showing of irreparable injury is necessary. *Topanga Press, Inc. v. City of Los* Angeles, 989 F.2d 1524, 1528-29 (9th Cir. 1993). Plaintiffs have met the requirements for a preliminary injunction.

I. DEFENDANTS DO NOT REFUTE PLAINTIFFS' SHOWING OF LIKELIHOOD OF SUCCESS ON THEIR CLAIMS

Plaintiffs have established, and Defendants' Opposition tacitly concedes, that SB 277 violates Plaintiffs' fundamental rights and irreconcilably conflicts with the California and Federal Constitutions, as well as numerous state and federal laws.

A. Strict Scrutiny Applies to SB 277 Because SB 277 Deprives Plaintiffs of Fundamental Rights and Suspect Classifications Are Issue

Education is a fundamental right guaranteed by the California Constitution. *Serrano I*, 5 Cal. 3d at 608-09 ("the distinctive and priceless function of education in

our society warrants, indeed compels, our treating it as a 'fundamental interest"). Defendants do not contest that education is a fundamental right and merely claim that its violation under SB 277 is justified without citing to a single case that has upheld denial of education to California students. Opp., Doc. 30, at 16-17. Defendants also do not refute Plaintiffs' evidence that SB 277, by its homeschooling exemption, implicates the suspect classifications of socioeconomic status and national origin. *Serrano I*, 5 Cal. 3d at 597, 614. Thus, strict scrutiny applies to SB 277 and, as discussed in detail in Plaintiffs' Motion and below Defendants' Opposition falls far short of overcoming strict scrutiny.

B. *Jacobson* and its Progeny Do Not Help Defendants Overcome Strict Scrutiny

Defendants' primary defense of SB 277 relies on *Jacobson v. The Commonwealth of Massachussetts*, 197 U.S. 11 (1905) and its progeny generally upholding vaccine mandates. But Defendants' reliance on *Jacobson* is misplaced.

As a threshold matter, SB 277 did not enact a vaccine mandate. It eliminated PBEs from the State's existing vaccine mandates by repealing Health and Safety Code section 120365. Indeed, California's vaccine mandates, codified in Health and Safety Code sections 120325(a)(1) - (10) and 120335(a)(1) - (10), existed under the *status quo ante* and were unchanged by SB 277. Plaintiffs do not ask the Court to invalidate those mandates. Rather, they seek an injunction of SB 277's repeal of PBEs, allowing children with PBEs to attend school pending resolution of this case. Accordingly, cases focused on vaccine mandates are irrelevant to a constitutional analysis of SB 277.

Furthermore, *Jacobson* and its progeny do not support Defendants' position. In fact, *Jacobson* expressly warns against legislation like SB 277. In *Jacobson*, the Court upheld the state's right to levy a $5.00 fine (approximately $122 dollars today) against Jacobson for refusing a smallpox vaccine during an epidemic. Jacobson was

not excluded from society and denied fundamental rights. Most importantly, even in the absence of strict scrutiny – which post-dates *Jacobson* – the Supreme Court warned of overbroad, oppressive legislation like SB 277. *Jacobson*, 197 U.S. at 38 ("the police power of a state...may be exerted in such circumstances, or by regulations so arbitrary and oppressive...as to justify the interference of the courts to prevent wrong and oppression"). Thus, a fair reading of *Jacobson* demonstrates that it requires public health necessity, proportionality, harm avoidance, and fairness in the exercise of a state's police power. SB 277, by contrast, is unnecessary, draconian, punitive legislation that constitutes precisely the kind of abuse of police power that justifies the "interference of courts to prevent wrong and oppression." *Id.*

None of the other post-*Jacobson* cases Defendants cite support the repeal of PBEs and permanent expulsion of children from school. For example, *Phillips v. City of New York*, 775 F.3d 538, 543 (2nd Cir. 2015) and *Maricopa County Health Dept. v. Harmon*, 750 P.2d 1364 (Ariz. 1987) upheld temporary – ***not permanent*** – exclusion of children from school during an outbreak. As such, those cases are consistent with pre-SB 277 California law which allowed for the temporary exclusion of children with PBEs during an outbreak.

Each of the remaining cases Defendants cite is inapposite or distinguishable. The California cases, *Abeel v. Clark*, 84 Cal. 226 (1890), *French v. Davidson*, 143 Cal. 658 (1904), and *Williams v. Wheeler*, 23 Cal. App. 619, 625 (1913) all arose in the context of vaccination for one disease (smallpox) and do not include denial of the fundamental right to education or the application of strict scrutiny. Similarly, *Zucht v. King*, 260 U.S. 174 (1922) dealt only with vaccination for smallpox and was decided on procedural grounds with no constitutional analysis. The *dicta* Defendants rely on in *Prince v. Massachusetts*, 321 U.S. 158 (1944), does not support SB 277's repeal of PBEs and denial of education. Moreover, since most adults in California are not subject compulsory vaccination, *Prince* would prohibit compulsory vaccination for their children as well. *See Prince*, 321 U.S. 158, 166 ("[a parent] cannot claim

freedom from compulsory vaccination for the child **more than for himself** on religious grounds") (emphasis added). In addition to being misplaced, Defendants' reliance on *Prince* is ironic. *Prince* applied the doctrine of *parens patriae* to keep children in school, while Defendants use it to bar children permanently from school.

Defendants' reliance on *Boone v. Boozman*, 217 F. Supp. 2d 938 (E.D. Ark. 2002), is particularly troubling. Defendants neglect to advise the Court that *Boone* was appealed to the Eighth Circuit where the appeal was dismissed as moot because, in the interim, the Arkansas legislature enacted broad religious and philosophical exemptions to Arkansas's vaccination mandate (Ark. Code Ann. 6-18- 702(d)(4).). *See McCarthy v. Ozark School Dist.*, 359 F.3d 1029 (2004). Thus, *Boone* has, in effect, been superseded by statute.

Finally, cases from the only two jurisdictions other than California that do not have a philosophical or religious exemption do not support Defendants. Neither *Workman* v. *Mingo County Sch.,* 667 F. Supp. 2d 679 (S.D. W. Va. 2009), *aff'd*, *Workman v. Mingo County Bd. of Educ.*, 419 F. App'x 348, 353-54 (4th Cir. 2011) (unpublished) nor *Brown v. Stone*, 378 So.2d 218 (1979), *cert. denied* 449 U.S. 887 (1980) address denial of the fundamental right to education or apply strict scrutiny.[3]

As the foregoing demonstrates, the cases Defendants cite do not address Plaintiffs' claims or the instant Motion and are not relevant to an analysis of whether the State's repeal of California's PBE statute and resulting ***permanent*** exclusion of healthy children with PBEs from school is constitutional, where various fundamental rights including the right to education are denied. In fact, these cases, when properly analyzed, support the relief Plaintiffs seek.

[3] West Virginia has never had religious or philosophical exemptions. In Mississippi, the *Brown* Court, in a strained equal protection analysis, struck a religious exemption that applied only to members of religions "whose religious teachings require reliance on prayer or spiritual means of healing." *Brown*, 378 So.2d at 219. In any event, religious exemptions that are limited to certain religions and do not allow for sincere and genuine personal religious beliefs are unconstitutional. *See Sherr v. Northport-East Northport Union Sch. Dist.*, 672 F. Supp. 81, 91-92 (E.D.N.Y. 1987). That was not the case with California's PBE.

C. Defendants Misconstrue Plaintiffs' Free Exercise Claims

As a preliminary matter, strict scrutiny, not rational basis review, applies to Plaintiffs' Free Exercise claims, because Plaintiffs assert "hybrid rights." *See Empl. Div. Oregon Dept. of Human Res. v. Smith*, 494 U.S. 872, 881-82 (1990); *Thomas v. Anchorage Equal Rights Comm'n*, 165 F.3d 692, 707 (9th Cir. 1999), *rev'd on other grounds en banc*, 220 F.3d 1134 (9th Cir. 2000). Defendants impermissibly separate Plaintiffs' constitutional claims and fail to address the "hybrids rights" strict scrutiny analysis, thereby waiving their arguments. Moreover, Defendants are wrong, both legally and factually, in their analysis of Plaintiffs' Free Exercise claims. Religious claims need not be based on teachings of a particular religious sect as Defendants contend, but can be grounded in an individual's sincere and genuine religious beliefs. *See Sherr v. Northport-East Northport Union Sch. Dist.*, 672 F. Supp. 81, 91-92 (E.D.N.Y. 1987); *Maier v. Besser*, 72 Misc. 2d 241, 341 N.Y.S.2d 411 (Sup. Ct. Onondaga Cty. 1972). Defendants are also wrong that Free Exercise does not "protect personal beliefs." It is axiomatic that "the protections of the Free Exercise Clause pertain if the law at issue discriminates against some or all religious beliefs." *Church of the Lukumi Babalu Aye, Inc. v. City of Hialeah*, 508 U.S. 520, 532 (1993). First Amendment jurisprudence explicitly protects views both secular and religious in nature. *See Callahan v. Woods*, 658 F.2d 679, 684 (9th Cir.1981) ("a coincidence of religious and secular claims in no way extinguishes the weight appropriately accorded the religious one"). A person may not be compelled to choose between the exercise of his religious beliefs and participation in a public program. *Everson v. Board of Education*, 330 U.S. 1, 16 (1947). Plaintiffs raise Free Exercise claims and pursuant to the applicable hybrid rights analysis, these claims require strict scrutiny review, which Defendants cannot overcome.

D. Defendants Fail to Address Plaintiffs' Equal Protection Claims

Plaintiffs argue that Defendants have violated equal protection by impermissibly creating classes of children who are excluded from school and treated

differently than others who are similarly situated. Defendants fail to address this issue instead arguing, off topic, that the mandates themselves are applied uniformly. Defendants concede that Plaintiffs' children are being deprived of their fundamental right to go to school and that children with IEPs are being treated differently across the state. Defendants thus admit violating equal protection. Defendants do not address why SB 277 exempts children who are homeschooled, in independent study or who have IEPs. Nor do Defendants address why children with disabilities who have Section 504 plans are not exempt from SB 277 while children with disabilities who have IEPs are exempt. Finally, Defendants do not address why for each of the next six years, kindergarten and seventh grade students with PBEs will be excluded from school under SB 277's "checkpoint" scheme, while children with PBEs in all other grades remain in school. Education is a fundamental right and SB 277 denies different categories of children that right at different times, violating equal protection.

E. The State Fails to Meet Its Burden Under Strict Scrutiny

Because SB 277 deprives children of the fundamental right to education, implicates the suspect classification of socioeconomic status, and unduly burdens other fundamental rights, strict scrutiny applies, placing the burden on the State to establish that a compelling state interest exists for SB 277 and that SB 277 is necessary, narrowly tailored and the least restrictive means to meet that interest. *Serrano I*, 5 Cal. 3d at 597. The State has failed to satisfy this burden.

1. Defendants Have Not Met Their Burden of Establishing A Compelling Interest For SB 277

The State has failed to show a compelling state interest to justify its complete abdication of its constitutional mandate to provide education to all California children. *Butt v. State of California*, 4 Cal. 4th 668, 685 (1992) ("The State itself bears the ultimate authority and responsibility to ensure that its district-based system of common schools provides basic equality of educational opportunity"). Defendants point to absolutely nothing that justifies removing PBEs and permanently barring

thousands of students from school. Defendants have also failed to meet their burden of demonstrating that SB 277 serves any necessary public health goal. In particular, as shown in Plaintiffs' Motion and herein, there is no public health justification, either rational or compelling, to support the patchwork of distinctions made under SB 277 and there is no public health emergency warranting even a temporary exclusion of students from schools, let alone SB 277's draconian, permanent result. Children with PBEs are not perpetual carriers of dangerous contagions and the State's treatment of them as such is unlawful and prohibited.[4]

2. Defendants Have Failed To Demonstrates that SB 277 Is Necessary, Narrowly Tailored, and The Least Restrictive Means of Achieving A Compelling State Interest

As demonstrated in Plaintiffs' Motion and herein, even assuming Defendants established a compelling state interest – which they have failed to do – SB 277 is not necessary, narrowly tailored or the least restrictive means of achieving that interest. In fact, the only portion of this prong that Defendants try to address, as shown below, is the "narrow tailoring," but their argument is limited to the fact that the legislation has a medical exemption and a provision excluding homeschooled children from the mandate. That is not narrow tailoring. The homeschool provision is not an exception but rather a punishment for those students who have not met the State's rigid vaccination mandate.

Defendants' fail to oppose Plaintiffs' evidence that the PBE rate in California was declining after AB2109 imposed conditions on the assertion of PBEs. Motion, Doc. 14-1, at 16. For that reason and the foregoing arguments, the State has not shown that SB 277 was necessary at a time when PBE rates were dropping, the state

[4] SB 277's permanent expulsion of thousands of children from school without due process is unprecedented and unsupportable. Even children who are expelled for cause (violence or harassment) are entitled to due process and may attend another school or receive an education program provided by their schools. *See, e.g.*, Calif. Educ. Code §§ 48915.1, 48915.2, 48916, 48916.1; see also https://www.aclunc.org/our-work/know-your-rights/school-discipline (Reply RJN Ex. 11).

demonstrated its ability to easily contain an outbreak of measles that originated in the most populous place in the entire state, and California's vaccination rates were at an "all time high" with schools that were "well-protected" from "vaccine-preventable" diseases according to CDPH.

Defendants try to argue that students have a right to attend safe schools and that the choice of the ten vaccines to mandate is a narrow tailoring designed to serve this interest. As a general proposition, Plaintiffs do not dispute that school safety is an important issue. However the State has introduced no admissible evidence to support their assertion that healthy children with PBEs endanger school safety or that school safety is assured by SB 277, neither of which is true. Defendants cannot argue that SB 277's permanent exclusion of healthy children from school is narrowly tailored or necessary for public health when pre-SB 277 law allowed for the temporary exclusion of children with PBEs during outbreaks.

SB 277 is unjustifiable. It is a draconian, overbroad, extreme measure that provides no public health benefit while depriving tens of thousands of children of their fundamental right to education and undermining the State's own compelling interest in educating its children. *Serrano I*, 5 Cal.3d at 606 ("society has a compelling interest in affording children an opportunity to attend school").

F. SB 277 Violates State and Federal Disability Laws

As an initial matter, there is no justification for Defendants' argument that the only claims for which injunctive relief is appropriate are those involving constitutional violations. *See* Opp., Doc. 30, at 24. As shown below, the severity of the violations of disability laws is sufficient grounds to support injunctive relief here. Substantively, Defendants misapprehend Plaintiffs' disability claims and fail to refute Plaintiffs' evidence entitling them to injunctive relief.

1. The State Refuses To Provide Guidance To Allow The Admission of Students with IEPs

While Defendants admit that SB 277 exempts students with IEPs, Defendants still have inexplicably failed to provide guidance to the districts to enroll students with IEPs. Plaintiffs allege that SB 277, as applied, violates IDEA and that DOE is obligated, as part of its non-delegable duty under the State Constitution and under Federal law, to ensure equal access to schools for students with IEPs. *See Butt, supra*. Plaintiffs unquestionably have a private right of action against Defendants and where, as here, systemic violations impacting thousands of students are alleged, exhaustion would be futile and is not required. *See, e.g.*, *Honig v. Doe*, 484 U.S. 305, 327 (1988); *Hoeft v. Tucson Unified Sch. Dist.*, 967 F.2d 1298, 1303 (9th Cir. 1992; *Morgan Hill Concerned Parents Assoc. v. Calif. Dept. of Educ.*, No. 2:11-cv-3471-KJM-AC, 2013 WL 1326301, at *8 (E.D. Calif. March 29, 2013).

2. Defendants Fail to Refute Plaintiffs' Section 504 claims

As with with IEPs, students with Section 504 plans are entitled to a Free and Appropriate Public Education under federal law. However, unlike IEP students, there is no exception in SB 277 to protect their rights. As demonstrated in Plaintiffs' Motion and herein, this violates the equal protection rights of students with 504 plans.

Defendants misstate Plaintiffs' claims concerning discrimination under Section 504 and the ADA. Plaintiffs do not allege that vaccine mandates are applied differently to students with disabilities. Rather, Plaintiffs demonstrate that the State's treatment of children with PBEs as inherently infectious and contagious and its exclusion of these children from school based on fear of contagion places these students in a protected category under the ADA, Section 504 and California disability laws. Defendants' entire Opposition is an admission of Defendants' treatment of Plaintiffs' children as vectors of "dangerous diseases" who threaten the public with "imminent harm." Thus, based on Defendants' own admissions, Plaintiffs have a

strong likelihood of success under the Section 504 and ADA claims, entitling them to injunctive relief.

II. DEFENDANTS CONCEDE THAT PLAINTIFFS WILL BE IRREPARABLY HARMED

Defendants do not contest that Plaintiffs will be irreparably harmed in the absence of an injunction and therefore have conceded the irreparable harm prong. Plaintiffs have made a substantial showing of irreparable injury, including violations of constitutionally protected rights. Motion, Doc. 14-1, at 22-24.

To the extent Defendants argue that there is no irreparable harm based on alleged delay by Plaintiffs in moving for injunctive relief, *see* Opp., Doc. 30, at 8, they are incorrect. Defendants argue that because parents could not file PBEs after January 1, 2016, the *status quo* changed on that day and Plaintiffs delayed several months in moving for relief. This is a frivolous argument. Defendants selectively read SB 277, which specifically provides that PBEs filed before January 1, 2016 stay in effect until July 1 2016: " . . . on and after July 1, 2016, the governing authority shall not unconditionally admit to any of those institutions specified in this subdivision for the first time, or admit or advance any pupil to 7th grade level, unless the pupil has been immunized for his or her age as required by this section." Health and Safety Code § 120335(g)(3). Thus, irreparable injury occurs – and grounds for injunctive relief exist – when children are denied admission.[5] In its July 5, 2016 Order, Doc. 4, denying Plaintiffs' motion for a TRO, this Court recognized that Plaintiffs are harmed when the fall semester begins and they cannot attend school. Thus, contrary to Defendants' claims, Plaintiffs' motion is timely and ripe for adjudication.

[5] *See* Reply RJN Ex. 12, which includes school calendars from various of Plaintiffs' school districts demonstrating that children on traditional school calendars are returning to school this month, many in just a few days.

III. THE BALANCE OF HARDSHIPS FAVORS PLAINTIFFS

The balance of hardships tips overwhelmingly toward Plaintiffs who, as demonstrated in their Motion, face a tremendous burden in loss of their children's right to an education, forced homeschooling against their will, as well as potential truancy charges and child removal if they are unable to homeschool. They face loss of jobs and resultant financial crises, and the possibility of moving out of state to secure their rights. These decisions, including the possibility of having to vaccinate their children to obtain education in violation of their fundamental rights, create tremendous hardship.

Conversely, there is no hardship to Defendants. Particularly, Defendants' discriminatory and prejudicial contentions notwithstanding, Plaintiffs' healthy children pose no threat that the State is attempting to prevent. Nor does reinstating the procedures used under AB 2109, the *status quo ante*, pose a hardship. Schools and medical professionals are familiar with PBEs, which existed for 55 years prior to SB 277. CDPH would be required to make the PBE form, Reply RJN Ex. 13 and its AB 2109 Frequently Asked Questions available on their website. No change to the CCRs would be needed, as CDPH has never repealed the CCRs that provide for PBEs. In fact, current law, as set forth in the CCRs specifically provides for PBEs. The State would simply stop asking schools to violate the CCRs. Finally, given the disarray in the state caused by Defendants' lack of guidance and inconsistent information, an injunction will restore order to schools and families.

IV. PUBLIC INTEREST WEIGHS IN PLAINTIFFS' FAVOR

Defendants also fail to address the public interest prong of the preliminary injunction analysis. Education is one of the most important rights under federal and California law. Keeping children in school undoubtedly serves the public interest both in the short and long term. There is no public health reason to override fundamental rights. The *status quo ante* has provided more than adequate protection for the health of Californians for more than fifty-five years.

V. DEFENDANTS PREMATURELY RAISE ARGUMENTS CONCERNING PLANTIFFS' MEDICAL RECORDS CLAIMS

Defendants have raised several arguments concerning Plaintiffs' claims with respect to medical records and the expenditure of state funds that are not properly before the Court. While Plaintiffs' claims are significant and are addressed in detail in Plaintiffs' First Amended Complaint, they were not a basis for Plaintiffs' Motion. Accordingly, it is improper for Defendants to raise these arguments in opposition and Plaintiffs do not address them in reply.

CONCLUSION

Plaintiffs respectfully request that the Court preliminarily enjoin SB 277 and preserve the *status quo ante* during the pendency of this action. The California Supreme Court recognized, 45 years ago, that "society has a compelling interest in affording children an opportunity to attend school," *Serrano v. Priest*, 5 Cal.3d at 602, and that education is "the bright hope for entry of the poor and oppressed into the mainstream of American society." *Id.* SB 277 is a stark departure from California's proud history of championing education, a legislative mistake that should not cost tens of thousands of children their education while Plaintiffs work to correct it. Children across the state are returning to their classrooms. Plaintiffs respectfully request that the Court grant their Motion and allow their children to join their peers.

DATED: August 5, 2016

Respectfully submitted,

By: */s/ James S. Turner*
James S. Turner
Betsy E. Lehrfeld
Robert T. Moxley
Kimberly M. Mack Rosenberg
Carl M. Lewis

Attorneys for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on August 5, 2016, I electronically filed the following document with the Clerk of the Court by using the CM/ECF system, on behalf of all Plaintiffs:

PLAINTIFFS' REPLY TO STATE DEFENDANTS' OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION.

I certify that all participants in the case are registered CM/ECF users and they will be served by the CM/ECF system.

I declare under penalty of perjury under the laws of the State of California the foregoing is true and correct and that this declaration was executed on August 5, 2016, at Washington, D.C.

/s/ James S. Turner

James S. Turner, Declarant

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ANA WHITLOW, et al., Plaintiffs, vs. STATE OF CALIFORNIA, DEPARTMENT OF EDUCATION, et al., Defendants.	Case No. 3:16-cv-01715-DMS-BGS **PLAINTIFFS' REQUEST TO TAKE JUDICIAL NOTICE IN FURTHER SUPPORT OF PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION AND IN REPLY TO STATE DEFENDANTS' OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION**

Plaintiffs hereby respectfully request that, pursuant to Rule 201 of the Federal Rules of Civil Procedure, the Court takes judicial notice of the following:

1. New York State Education Department, Office of Counsel, Decision No. 16,805, *N.C. v. New York City Dept. of Educ.*, August 3, 2015, available at http://www.counsel.nysed.gov/Decisions/volume55/d16805, accessed on August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "1."

2. Centers for Disease Control, Vaccine Excipient & Media Summary, Appendix B, pages B7-B10, dated April 15, 2015, available at https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf , accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "2."

3. Manufacturer product inserts for the following vaccines:
   a) Pentacel (Diphtheria, Tetanus, Pertussis, Polio and Haemophilus B) (Sanofi Pasteur), available at https://www.vaccineshoppe.com/image.cfm?doc_id=11169&image_type=product_pdf, accessed August 5, 2016;
   b) ProQuad (Measles, Mumps, Rubella and Varicella) (Merck & Co., Inc.), available at https://www.merck.com/product/usa/pi_circulars/p/proquad/proquad_pi.pdf, accessed August 5, 2016,

c) Varivax (Varicella) (Merck & Co.), available at https://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf, accessed August 5, 2016,
d) MMRII (Measles, Mumps, Rubella) (Merck & Co., Inc.), available at https://www.merck.com/product/usa/pi_circulars/m/mmr_ii/mmr_ii_pi.pdf, accessed August 5, 2016,

true and correct copies of which are attached hereto as Exhibit "3."

4. Pontifical Academy for Life statement "Moral Reflections on Vaccines Prepared from Cells Derived from Aborted Human Foetuses," available at http://www.academiavita.org/_pdf/documents/pav/moral_relflections_on_vaccines_en.pdf, accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "4."

5. True and correct copies of the following documents are attached hereto as Exhibit "5":
   a) Felice J. Freyer, "Harvard mumps outbreak grows to 40" (April 26, 2016), accessed on June 29, 2016 at https://www.bostonglobe.com/metro/2016/04/26/harvard-mumps-outbreak-grows-cases/dLW4RTngYHl2elJivMO3LL/story.html;
   b) Matt McCullock, "Whooping Cough Cases on the Rise" (August 10, 2015), available at http://www.texomashomepage.com/news/local-news/whooping-cough-cases-on-the-rise, accessed August 5, 2016;
   c) "6 University of Missouri Students Confirmed with Mumps" (July 28, 2015), available at http://fox2now.com/2015/07/28/6-university-of-missouri-students-confirmed-with-mumps/, accessed August 5, 2016;
   d) "Mumps outbreak sweeps Long Beach; affected residents had already been vaccinated" (August 1, 2016), available at http://www.fios1news.com/longisland/long-beach-mumps-outbreak#.V6UaOLWGGTX, accessed August 5, 2016;
   e) Nsikan Akpan, "Measles Outbreak Traced to Fully Vaccinated Patient for First Time" (April 11, 2014), available at http://www.sciencemag.org/news/2014/04/measles-outbreak-traced-fully-vaccinated-patient-first-time, accessed August 5, 2016.

6. "California Department of Health: Measles," last revised 2/2/2016, available at https://www.cdph.ca.gov/HEALTHINFO/DISCOND/Pages/Measles.aspx,

accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "8."

7. Office of Administrative Law, About California Code of Regulations, available at http://www.oal.ca.gov/ccr.htm, accessed August 2, 2016, a true and correct copy of which is attached hereto as Exhibit "7."

8. Letter from Sarah Royce, M.D., MPH, Chief, Center for Infectious Diseases, Division of Communicable Disease Control, Immunization Branch, California Department of Public Health, dated July 2, 2015 to "Interested Parties," Subject: SB 277, available at http://www.immunizeca.org/wp-content/uploads/2015/07/SB-277-Letter-2016-Effective-Date-070215-final.pdf, accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "9."

9. California Conference of Local Health Officers, Board of Directors Meeting Minutes (February 4, 2016), available at https://www.cdph.ca.gov/programs/cclho/Documents/February4,2016BoardMeetingMinutes.pdf, accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "10."

10. PowerPoint Presentation titled "SB 277 –Update: CCLHO, February 4, 2016," available at https://www.cdph.ca.gov/programs/cclho/Documents/RoyceSB277HORoles.pdf accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "11."

11. ACLU of Northern California, "Know Your Rights: Suspensions, Expulsions, and Involuntary Transfers," available at https://www.aclunc.org/our-work/know-your-rights/school-discipline, available at https://www.aclunc.org/our-work/know-your-rights/school-discipline, accessed August 5, 2016, a true and correct copy of which is attached hereto as Exhibit "11."

12. True and correct copies of 2016-17 school calendars from the following districts, attached hereto as Exhibit "12," all accessed August 5, 2016:
    a) Cajon Valley Union School District, available at http://www.cajonvalley.net//site/UserControls/Calendar/CalendarPrint.aspx?ModuleInstanceID=10913&PageID=2&DomainID=4&Date=1&Month=7&Year=2016&View=month

b) Loomis Union School District, available at https://d3jc3ahdjad7x7.cloudfront.net/SaoEVL89YnCvM4yBZwBo2OyXYsMT8vVkteRapEBi1u8yIeIL.pdf
c) Madera Unified School District, available at http://www.madera.k12.ca.us/site/Default.aspx?PageID=282
d) Placerville Union School District, available at http://www.pusdk8.us/page/2
e) Sacramento City Unified School District, available at http://www.scusd.edu/sites/main/files/file-attachments/final_board_approved_2016-17_traditional_school_year_calendar_5.26.16_v3.pdf
f) San Diego Unified School District, available at https://www.sandiegounified.org/schools/sites/default/files_link/schools/files/Domain/201/1617-calendar-traditional.pdf
g) San Rafael City Schools, available at http://srcs-ca.schoolloop.com/file/1356610548397/1229223258692/1126683310629079484.pdf
h) Santa Barbara Unified School District, available at http://www.sbunified.org/districtwp/wp-content/uploads/2013/01/2016-17-Traditional-School-Calendar.pdf
i) Vista Unified School District, available at http://vistausd-ca.schoolloop.com/file/1346929853202/1346929755224/5831040524364873207.pdf

13. California Department of Public Health Personal Belief Exemption form used under AB 2109 (California Health and Safety Code § 120365), a true and correct copy of which is attached hereto as Exhibit "13."

DATED: August 5, 2016

Respectfully submitted,

By: */s/ James S. Turner*
James S. Turner
Betsy E. Lehrfeld
Robert T. Moxley
Kimberly M. Mack Rosenberg
Carl M. Lewis

Attorneys for Plaintiffs

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I hereby certify that on August 5, 2016, I electronically filed the following document with the Clerk of the Court by using the CM/ECF system, on behalf of all Plaintiffs:

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/s/ James S. Turner
James S. Turner, Declarant

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Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ANA WHITLOW, et al.,

Plaintiffs,

vs.

STATE OF CALIFORNIA, DEPARTMENT OF EDUCATION, et al.,

Defendants.

Case No. 3:16-cv-01715-DMS-BGS

NOTICE OF LODGMENT AND LODGMENT OF EXHIBITS IN FURTHER SUPPORT OF PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION AND IN REPLY TO STATE DEFENDANTS' OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE, that PLAINTIFFS lodged the following exhibits in further support of Plaintiffs' Motion for Preliminary Injunction and in reply to State Defendants' opposition to Motion for Preliminary Injunction.

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DATED: August 5, 2016

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/s/ James S. Turner
James S. Turner, Declarant

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New York State
EDUCATION DEPARTMENT
OFFICE OF COUNSEL

Decision No. 16,805

Commissioner's Decisions | Search Decisions

Appeal of N.C., on behalf of her son C.C., from action of the New York City Department of Education regarding immunization.

Decision No. 16,805

(August 3, 2015)

Zachary W. Carter, Esq., Corporation Counsel, attorney for respondent, Omar H. Tuffaha, Esq., of counsel

ELIA, Commissioner.--Petitioner appeals the determination of the New York City Department of Education ("respondent") that her son, C.C.("the student"), is not entitled to an exemption from the immunization requirements of Public Health Law ("PHL") §2164. The appeal must be sustained.

By letter dated July, 1, 2013, petitioner requested a religious exemption on behalf of the student, who was attending respondent's public school. In her letter, petitioner states that she "used to faithfully vaccinate" the student and that he was up-to-date on all of his vaccinations until she had a "change of heart and mind on the subject ..." of vaccinations in April 2011 after speaking to a friend who told petitioner that the practice of vaccination "goes against the Christian faith." The student has not received the required second dose of the MMR vaccine (MMR #2), which the record indicates is the only remaining required vaccination that her son has not received at the time of this appeal. Petitioner describes wrestling with the concept of vaccinations "quite a bit after [the student] was diagnosed with autism" and states that "after researching on a few Bible and Christian blogs" she determined that her friend "was right about vaccination." Petitioner identifies herself as Russian Orthodox and explains that although she emigrated from Russia, she spent her childhood in a country that did not condone religious freedoms yet she developed her strong faith in God from her maternal grandmother who "never abandoned Christian faith" and "introduced me and my sister to God." Petitioner states "I remember her reading us passages from the Bible and talking to us about what these passages meant."

Petitioner states that her most compelling reasons for objection to vaccination are what she deems her "faith issue." Petitioner states that "our fate is in the hands of our Lord, even if He decides that we should have a flu or measles." She further states that "mortality is, and should be, in God's hands" and thus "vaccination intercedes upon God's rightful realm, as if being in God's care alone is not assurance enough for us." In addition, petitioner states that she objects to vaccinations because they "contain cells of animal

origin" which is counter to religious teachings that "blood [is] sacred" and should not be mixed "with foreign blood or any other impure matters." Petitioner further states that the "final straw" is that "a number of vaccines contain cells from aborted fetuses" and "abortion is clearly considered a mortal sin and is [an] abhorrent act to any Christian."

In support of her position, in petitioner's letter dated July 1, 2013, petitioner provided a link to the Centers for Disease Control and Prevention ("CDC") website which appears to provide a list of ingredients in vaccinations, including the MMR #2. Petitioner states:

> ...as a person of faith I cannot be knowingly associated with any person or entity who directly or indirectly utilizes products of such hideous acts. The vaccine manufacturers [sic] use of aborted fetal cells in its products and research means that I cannot associate with them or support them financially (by buying their products), for such support would make me complicit to their sin and answerable to God for this violation.

By memorandum dated August 20, 2013, the Health Service Coordinator ("coordinator") in respondent's Office of School Health ("OSH") denied petitioner's request, stating that "the documentation you submitted is inadequate to warrant an exemption and does not substantiate a finding that you hold genuine and sincere religious beliefs which are contrary to immunization." The memorandum provided information about how to appeal the determination, which petitioner did by requesting an interview with the Health Liaison ("liaison") for the Children First Network ("CFN").

Petitioner met with the liaison on September 3, 2013. In response to the liaison's questions about her sincerely held religious beliefs, petitioner largely repeated and referred to the contents of her original letter.

By memorandum dated September 23, 2013, the coordinator denied petitioner's appeal, stating that the "documentation you submitted and the information provided during the appeal interview do not substantiate a finding that you hold genuine and sincere religious beliefs which are contrary to immunization" and that "[The student] has all of the required vaccines except for MMR #2." This appeal ensued. Petitioner's request for interim relief was granted on November 7, 2013.

Petitioner contends that her objections to immunizations are based on genuine and sincerely held religious beliefs and seeks a determination that the student is entitled to a religious exemption from the immunization requirements under PHL §2164. Petitioner also claims that respondent failed to provide her with specific reasons for the denial of her request and that the denial was arbitrary and capricious. Petitioner further alleges that her constitutional rights have been violated and "contends that the process by which NYC DOE and OSH processed her religious exemption applications is fraudulent and violated her right to due process."

Respondent contends that petitioner failed to provide sufficient information to support a religious exemption and that its determination was rational, not arbitrary or capricious, and in all respects proper. Respondent further asserts that petitioner's objections to immunizations are not based on genuine and sincerely held religious beliefs and that petitioner failed to meet her burden of proof.

I must first address several procedural issues. An appeal to the Commissioner is not the proper forum to adjudicate novel issues of constitutional law or to challenge the constitutionality of a statute or regulation (Appeal of C.S., 49 Ed Dept Rep 106, Decision No. 15,971; Appeal of J.A., 48 id. 118, Decision No. 15,810; Appeal of Keller, 47 id. 224, Decision No. 15,677). A novel claim of constitutional dimension should properly be presented to a court of competent jurisdiction (Appeal of J.A., 48 Ed Dept Rep 118, Decision No. 15,810).

Therefore, to the extent that petitioner attempts to raise constitutional issues in regard to this appeal, I decline to consider such constitutional claims.

The purpose of a reply is to respond to new material or affirmative defenses set forth in an answer (8 NYCRR §§275.3 and 275.14). A reply is not meant to buttress allegations in the petition or to belatedly add assertions that should have been in the petition (Appeal of Caswell, 48 Ed Dept Rep 472, Decision No. 15,920; Appeal of Hinson, 48 id. 437, Decision No. 15,908; Appeal of Baez, 48 id. 418, Decision No. 15,901). Therefore, while I have reviewed the reply, I have not considered those portions containing new allegations or exhibits that are not responsive to new material or affirmative defenses set forth in the answer.

By letter dated December 19, 2013, petitioner submitted an additional memorandum of law in response to respondent's memorandum of law. Respondent objects to petitioner's additional memorandum of law for a number of reasons, including that it contains new allegations and requests for relief. Additional affidavits, exhibits and other supporting papers may only be submitted with the prior permission of the Commissioner (8 NYCRR §276.5). While this provision permits the submission of additional evidence, it cannot be used to add new claims against a respondent for which notice has not been provided (Appeals of Gonzalez, 48 Ed Dept Rep 405, Decision No. 15,898; Appeal of Marquette, et al., 48 id. 193, Decision No. 15,833). I will not accept materials that raise new issues and introduce new exhibits that are not relevant to the claims originally raised in the appeal (Appeals of Gonzalez, 48 Ed Dept Rep 405, Decision No. 15,898; Appeal of Marquette, et al., 48 id. 193, Decision No. 15,833). As noted above, petitioner requests that I accept her additional document because it addresses arguments contained in respondent's memorandum of law. However, I decline to consider any new issues, claims or evidence made against respondent that were not originally raised in the petition.

Petitioner further submitted additional papers entitled "Motion to Dismiss and Request for Summary Judgment" ("motion"). Although the Commissioner's regulations do not contemplate motions in appeals brought pursuant to Education Law 310 (Appeal of Alfano, et al., 39 Ed Dept Rep 229, Decision No. 14,224), I have consistently held that where, as here, a petitioner is proceeding without representation by counsel, a liberal interpretation of the rules is appropriate, particularly when respondent has presented no evidence of prejudice (Appeal of Cieslik, et al., 40 Ed Dept Rep 269, Decision No. 14,478; Appeal of Smith, 40 id. 172, Decision No. 14,452). I find that the purported motion addresses matters raised in the answer and responding affidavits and, thus, falls within the general category of an additional reply. However, I decline to consider any additional documents which argue new issues, claims and evidence made against respondent that were not originally raised in the petition.

Finally, petitioner provides an affidavit containing her own transcription of the September 3, 2013 interview with respondent's liaison, claiming that such recording was made intentionally in support of her exemption request because petitioner "did not know what to expect from this meeting." I note that §4506 of the Civil Practice Law and Rules provides that any evidence obtained by illegal eavesdropping is inadmissible in any hearing or proceeding before any department, officer, agency or other authority of the State. Under this section, an aggrieved party in a proceeding must make a motion before a justice of the Supreme Court in order to suppress the contents of an unlawfully recorded conversation. In this case, respondent made no such motion; however, respondent did raise a specific objection to the recording. I also note that, although the record contains a report of the liaison's questions and petitioner's responses at the September 3, 2013 interview, the record contains no sworn or written statement from the liaison regarding this conversation. On the other hand, petitioner submits the transcript as part of an affidavit in which she avers that such is the "complete conversation." Therefore, while I have considered this information as part of the record in this case, I have weighed it accordingly (cf. Appeal of a Student with a Disability, 52 Ed Dept Rep, Decision No. 16,491).

Turning to the merits, PHL §2164 prohibits a school from admitting a child without evidence that the child has received certain immunizations. However, §2164(9) provides:

> This section shall not apply to children whose parent, parents, or guardian hold genuine and sincere religious beliefs which are contrary to the practices herein required, and no certificate shall be required as a prerequisite to such children being admitted or received into school or attending school.

The determination of whether petitioner qualifies for a religious exemption requires the careful consideration of two factors: whether petitioner's purported beliefs are religious and, if so, whether such religious beliefs are genuinely and sincerely held (see Farina v. Bd. of Educ. of the City of New York, et al., 116 F Supp 2d 503). It is not necessary for persons to be members of a recognized religious organization whose teachings oppose inoculation to claim the statutory exemption (Sherr, et al. v. Northport-East Northport Union Free School Dist., et al., 672 F Supp 81). However, the exemption does not extend to persons whose views are founded upon medical or purely moral considerations, scientific or secular theories, or philosophical and personal beliefs (Farina v. Bd. of Educ. of the City of New York, et al., 116 F Supp 2d 503).

Whether a religious belief is sincerely held can be a difficult factual determination that must be made, in the first instance, by school district officials (Appeal of C.S., 49 Ed Dept Rep 106, Decision No. 15,971; Appeal of H.K. and T.K., 49 id. 56, Decision No. 15,957; Appeal of S.B., 48 id. 332, Decision No. 15,875). A parent/guardian who seeks a religious exemption must submit a written and signed statement to the school district stating that the parent/guardian objects to their child's immunization due to sincere and genuine religious beliefs which prohibit the immunization of their child (10 NYCRR §66-1.3[d]). If, after reviewing the parental statement, questions remain about the existence of a sincerely held religious belief, the principal or person in charge of a school may request supporting documents (10 NYCRR §66-1.3[d]).

In determining whether beliefs are religious in nature and sincerely held, school officials must make a good faith effort to assess the credibility and sincerity of petitioner's statements and may consider petitioner's demeanor and forthrightness. While school officials are not required to simply accept a statement of religious belief without some explanation, they similarly should not simply reject a statement without further examination (Appeal of C.S., 49 Ed Dept Rep 106, Decision No. 15,971; Appeal of H.K. and T.K., 49 id. 56, Decision No. 15,957; Appeal of S.B., 48 id. 332, Decision No. 15,875).

In an appeal to the Commissioner, a petitioner has the burden of demonstrating a clear legal right to the relief requested and the burden of establishing the facts upon which petitioner seeks relief (8 NYCRR §275.10; Appeal of Aversa, 48 Ed Dept Rep 523, Decision No. 15,936; Appeal of Hansen, 48 id. 354, Decision No. 15,884; Appeal of P.M., 48 id. 348, Decision No. 15,882).

Petitioner asserts that respondent failed to provide sufficient explanation of the reasons for denying her request for a religious exemption. To support her claim, petitioner relies on guidance from the New York State Education Department ("Department"), which states that a decision to deny a request for a religious exemption must be in writing and "the written communication must address the specific reasons for the denial; merely stating that the request does not demonstrate a sincerely held religious belief is not sufficient articulation." As described above, both the August 20, 2013 and the September 23, 2013 memoranda essentially stated that petitioner failed to demonstrate sincerely held religious beliefs which are contrary to immunization. The coordinator elaborates in her affidavit that "petitioner failed to provide sufficient documentation or information to substantiate a finding that petitioner held a genuine and sincere religious belief contrary to immunizations." Nevertheless, for purposes of this appeal, respondent has articulated a rationale for its determination, to which petitioner has had ample opportunity to respond and has indeed

Accordingly, I will not sustain the appeal solely on this ground and I need not address the merits of petitioner's argument on this issue as the appeal must be sustained for other reasons described below. However, I admonish respondent to provide parents with appropriate written communications articulating the specific reasons for the denial of religious exemptions in accordance with the Department's guidance.

Respondent disputes that petitioner's objection to vaccines are based on sincere and genuine religious beliefs. To support its position, respondent argues that petitioner has failed to show that her beliefs are religious in nature and has failed to put forth evidence that the Russian Orthodox Church in any way expresses opposition to vaccinations. Respondent also contends that petitioner's citations to biblical verses and texts do not warrant a finding that her beliefs are religious in nature. I agree with respondent that the record does not support a finding that the Russian Orthodox Church itself has taken the position that the use of vaccines is forbidden or prohibited; however, it is not necessary for persons to be members of a recognized religious organization whose teachings oppose inoculation to claim the statutory exemption (Sherr, et al. v. Northport-East Northport Union Free School Dist., et al., 672 F Supp 81). Furthermore, while I have generally held that mere citations to statements that are religious in nature, general statements about God, the perfection of the immune system, and citations to biblical verses and passages, without more, are not sufficient to establish genuine and sincere religious beliefs against immunization (see Appeal of B.R. and M.R., 50 Ed Dept Rep, Decision No. 16,250; Appeal of I.M. and G.M., 50 id., Decision No. 16,164; Appeal of C.S., 50 id., Decision No. 16,163). In the instant appeal, although petitioner cites to biblical texts and religious materials, she further explains and specifies the precise nature and origin of her beliefs as described in her own words in her July 1, 2013 exemption request. In addition, at the liaison meeting, petitioner explained her beliefs as outlined in her original exemption request. Her beliefs appear to be based on her own interpretation of the Bible in accordance with her Christian upbringing, are religious in nature, well-articulated, consistent and straightforward, at least with respect to the MMR vaccine at issue in this appeal. Other than her assertion that her son is autistic, which she does not attempt to link to her objections to immunizations, there is no evidence that petitioner's position is not religious in nature or based on philosophical, scientific, medical or personal preference.

Respondent further argues that in response to interview questions at the liaison meeting, petitioner acknowledged that she believes in other forms of medical intervention despite the fact that her stated rationale for objecting to vaccination is that man's fate is in God's hands and that vaccines "usurp God's power to decide our fate." However, the fact that petitioner would consent to medical treatment of a sick child is not necessarily determinative. Individuals need not oppose medical treatment per se to qualify for a religious exemption, but must assert only that they believe in reactive as opposed to proactive medical treatment (Lewis, et al. v. Sobol, et al., 710 F Supp 506). Similarly, the fact that petitioner's child was immunized in the past is not necessarily dispositive in determining whether the individual has genuine and sincere religious beliefs (Lewis, et al. v. Sobol, et al., 710 F Supp 506; Appeal of B.R. and M.R., 50 Ed Dept Rep, Decision No. 16,250) although it does have a bearing on the assessment of the sincerity of the alleged religious beliefs (see, Caviezel v. Great Neck Public Schools et al. 701 F Supp 2d 414).

To support her religious exemption request, petitioner contends that "the scriptures consider our blood sacred and specifically warn us against mixing it with foreign blood or any other impure matters." Petitioner states that she looked at the vaccine ingredients on the CDC website and "learned that vaccines contain cells of animal origin" and that is one of the reasons she objects to immunizations; however, these statements do not, in and of themselves, establish a sincerely held religious objection to immunization (see e.g. Appeal of O.M and R.M., 52 Ed Dept Rep, Decision No. 16,414; Appeal of L.S., 50 id., Decision No. 16,180).

Petitioner, however, also objects to immunizations based on her opposition to abortion, which is religious in nature and is based upon her interpretation of Bible teachings and doctrines as well as her upbringing in the Russian Orthodox religion (see Appeal of D.H., 52 Ed Dept Rep, Decision No. 16,425; Appeal of B.O-G., 51 id., Decision No. 16,294). Petitioner contends that, even if a specific vaccine does not contain aborted fetal cells, she is still opposed to it because all vaccines have been tainted by vaccine manufacturers who use aborted fetal cells in their products and research in related fields. She also alleges, however, that the MMR vaccine, the only vaccine at issue in this case, does contain human diploid cells that use aborted fetal cell lines.

Although, as respondent notes, petitioner's own interpretation of official Russian Orthodox Church teachings and doctrines may differ from those of the Russian Orthodox Church, the record indicates that her objection to certain immunizations is based on her opposition to abortion, which is religious in nature and genuine and sincerely held. The record also indicates that the Church strongly opposes abortion and that petitioner's opposition to all vaccinations is based on her own genuine and sincere religious beliefs about abortion. As noted above, the determination of whether petitioner qualifies for a religious exemption requires the careful consideration of two factors: whether petitioner's purported beliefs are religious and, if so, whether such religious beliefs are genuinely and sincerely held (see Farina v. Bd. of Educ. of the City of New York, et al., 116 F Supp 2d 503).

In support of her position, petitioner provided a link to the CDC website which contains a list of ingredients in vaccinations, including the MMR vaccine, and indicates that the MMR vaccine uses human diploid cell cultures that were first isolated from an aborted fetus. In addition, as part of her petition, petitioner submitted several articles and samples of current manufacturers' product inserts, including one from the manufacturer of the MMR vaccine, indicating use of human diploid aborted fetal cell lines with what appear to be website reference links to the same. While it is unclear whether petitioner provided these documents to respondent's coordinator or liaison prior to this appeal, petitioner's July 1, 2013 letter contained information regarding the link between the vaccines to which petitioner objects and aborted fetal tissue. In this appeal, respondent has not submitted evidence to rebut the linkage between the MMR vaccine and aborted fetal tissue. Thus, I find that the record in this proceeding contains evidence of a possible linkage between the MMR vaccine and the use of aborted fetal tissue, to which petitioner objects on religious grounds (see Appeal of B.O-G., 51 Ed Dept Rep, Decision No. 16,294).

Based on the record before me, I conclude that the weight of the evidence supports petitioner's contentions that her opposition to the MMR vaccine stems from sincerely held religious beliefs. Petitioner's assertion that she objects to all immunizations regardless of their use of human fetal tissue does undercut her reliance on a religious objection based on a linkage to the use of aborted fetal tissue (see e.g. Appeal of B.R. and M.R., 50 Ed Dept Rep, Decision No. 16,250). Based on the totality of the record in this appeal, however, I do not find that dispositive, as petitioner has produced unrebutted evidence of a linkage to the only vaccine at issue (cf. Appeal of B.R. and M.R., 50 Ed Dept Rep, Decision No. 16,250; Appeal of Y.R. and C.R., 50 id., Decision No. 16,165; Appeal of C.S., 50 id., Decision No. 16,163). Petitioner articulated and demonstrates a religious belief, and the record does not indicate that petitioner's position is based on philosophical, scientific, medical or personal preference. Furthermore, petitioner produced information relative to specific ingredients in vaccinations, including the MMR #2, in her July 1, 2013 exemption request which appears to provide the linkage between vaccines and aborted fetal tissue. I find that respondent fails to adequately explain its rejection of otherwise convincing evidence. I cannot, therefore, defer to respondent's assessment of petitioner's credibility to the extent such an assessment was made (Appeal of C.R. and C.R., 44 Ed Dept Rep 39, Decision No. 15,091).

THE APPEAL IS SUSTAINED.

IT IS ORDERED that respondent grant petitioner's son a religious exemption from the immunization requirement specified on this decision pursuant to Public Health Law §2164.

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Vaccine Excipient & Media Summary

Excipients Included in U.S. Vaccines, by Vaccine

This table includes not only vaccine ingredients (e.g., adjuvants and preservatives), but also substances used during the manufacturing process, including vaccine-production media, that are removed from the final product and present only in trace quantities.
In addition to the substances listed, most vaccines contain Sodium Chloride (table salt).

Last Updated February 2015
All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here. If in doubt, check the manufacturer's package insert.

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Adenovirus	sucrose, D-mannose, D-fructose, dextrose, potassium phosphate, plasdone C, anhydrous lactose, micro crystalline cellulose, polacrilin potassium, magnesium stearate, cellulose acetate phthalate, alcohol, acetone, castor oil, FD&C Yellow #6 aluminum lake dye, human serum albumin, fetal bovine serum, sodium bicarbonate, human-diploid fibroblast cell cultures (WI-38), Dulbecco's Modified Eagle's Medium, monosodium glutamate	March 2011
Anthrax (Biothrax)	aluminum hydroxide, benzethonium chloride, formaldehyde, amino acids, vitamins, inorganic salts and sugars	May 2012
BCG (Tice)	glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, Iron ammonium citrate, lactose	February 2009
DT (Sanofi)	aluminum potassium sulfate, peptone, bovine extract, formaldehyde, thimerosal (trace), modified Mueller and Miller medium, ammonium sulfate	December 2005
DTaP (Daptacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-Phenoxyethanol, Stainer-Scholte medium, modified Mueller's growth medium, modified Mueller-Miller casamino acid medium (without beef heart infusion), dimethyl 1-beta-cyclodextrin, ammonium sulfate	October 2013
DTaP (Infanrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium	November 2013
DTaP-IPV (Kinrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, Vero (monkey kidney) cells, calf serum, lactalbumin hydrolysate, polysorbate 80, neomycin sulfate, polymyxin B, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium	November 2013
DTaP-HepB-IPV (Pediarix)	formaldehyde, gluteraldehyde, aluminum hydroxide, aluminum phosphate, lactalbumin hydrolysate, polysorbate 80, neomycin sulfate, polymyxin B, yeast protein, calf serum, Fenton medium (containing bovine extract), modified Latham medium (derived from bovine casein), modified Stainer-Scholte liquid medium, Vero (monkey kidney) cells	November 2013
DTaP-IPV/Hib (Pentacel)	aluminum phosphate, polysorbate 80, formaldehyde, sucrose, gutaraldehyde, bovine serum albumin, 2-phenoxethanol, neomycin, polymyxin B sulfate, Mueller's Growth Medium, Mueller-Miller casamino acid medium (without beef heart infusion), Stainer-Scholte medium (modified by the addition of casamino acids and dimethyl-beta-cyclodextrin), MRC-5 (human diploid) cells, CMRL 1969 medium (supplemented with calf serum), ammonium sulfate, and medium 199	October 2013
Hib (ActHIB)	ammonium sulfate, formalin, sucrose, Modified Mueller and Miller medium	January 2014
Hib (Hiberix)	formaldehyde, lactose, semi-synthetic medium	March 2012
Hib (PedvaxHIB)	aluminum hydroxphosphate sulfate, ethanol, enzymes, phenol, detergent, complex fermentation medium	December 2010

Appendix B

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Hib/Hep B (Comvax)	yeast (vaccine contains no detectable yeast DNA), nicotinamide adenine dinucleotide, hemin chloride, soy peptone, dextrose, mineral salts, amino acids, formaldehyde, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, sodium borate, phenol, ethanol, enzymes, detergent	December 2010
Hib/Mening. CY (MenHibrix)	tris (trometamol)-HCl, sucrose, formaldehyde, synthetic medium, semi-synthetic medium	2012
Hep A (Havrix)	aluminum hydroxide, amino acid supplement, polysorbate 20, formalin, neomycin sulfate, MRC-5 cellular proteins	December 2013
Hep A (Vaqta)	amorphous aluminum hydroxyphosphate sulfate, bovine albumin, formaldehyde, neomycin, sodium borate, MRC-5 (human diploid) cells	February 2014
Hep B (Engerix-B)	aluminum hydroxide, yeast protein, phosphate buffers, sodium dihydrogen phosphate dihydrate	December 2013
Hep B (Recombivax)	yeast protein, soy peptone, dextrose, amino acids, mineral salts, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, formaldehyde, phosphate buffer	May 2014
Hep A/Hep B (Twinrix)	formalin, yeast protein, aluminum phosphate, aluminum hydroxide, amino acids, phosphate buffer, polysorbate 20, neomycin sulfate, MRC-5 human diploid cells	August 2012
Human Papillomavirus (HPV) (Cerverix)	vitamins, amino acids, lipids, mineral salts, aluminum hydroxide, sodium dihydrogen phosphate dehydrate, 3-O-desacyl-4' Monophosphoryl lipid A, insect cell, bacterial, and viral protein	November 2013
Human Papillomavirus (HPV) (Gardasil)	yeast protein, vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, sodium borate	June 2014
Human Papillomavirus (HPV) (Gardasil 9)	yeast protein, vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, sodium borate	December 2014
Influenza (Afluria)	beta-propiolactone, thimerosol (multi-dose vials only), monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, neomycin sulfate, polymyxin B, egg protein, sucrose	December 2013
Influenza (Agriflu)	egg proteins, formaldehyde, polysorbate 80, cetyltrimethylammonium bromide, neomycin sulfate, kanamycin, barium	2013
Influenza (Fluarix) Trivalent and Quadrivalent	octoxynol-10 (Triton X-100), α-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde, sodium deoxycholate, sucrose, phosphate buffer	June 2014
Influenza (Flublok)	monobasic sodium phosphate, dibasic sodium phosphate, polysorbate 20, baculovirus and host cell proteins, baculovirus and cellular DNA, Triton X-100, lipids, vitamins, amino acids, mineral salts	March 2014
Influenza (Flucelvax)	Madin Darby Canine Kidney (MDCK) cell protein, MDCK cell DNA, polysorbate 80, cetyltrimethlyammonium bromide, β-propiolactone, phosphate buffer	March 2014
Influenza (Fluvirin)	nonylphenol ethoxylate, thimerosal (multidose vial–trace only in prefilled syringe), polymyxin, neomycin, beta-propiolactone, egg proteins, phosphate buffer	February 2014
Influenza (Flulaval) Trivalent and Quadrivalent	thimerosal, formaldehyde, sodium deoxycholate, egg proteins, phosphate buffer	February 2013
Influenza (Fluzone: Standard (Trivalent and Quadrivalent), High-Dose, & Intradermal)	formaldehyde, octylphenol ethoxylate (Triton X-100), gelatin (standard trivalent formulation only), thimerosal (multi-dose vial only) , egg protein, phosphate buffers, sucrose	2014

B

Appendix B

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Influenza (FluMist) Quadrivalent	ethylene diamine tetraacetic acid (EDTA), monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gentamicin sulfate, egg protein	July 2013
Japanese Encephalitis (Ixiaro)	aluminum hydroxide, Vero cells, protamine sulfate, formaldehyde, bovine serum albumin, sodium metabisulphite, sucrose	May 2013
Meningococcal (MCV4-Menactra)	formaldehyde, phosphate buffers, Mueller Hinton agar, Watson Scherp media, Modified Mueller and Miller medium, detergent, alcohol, ammonium sulfate	April 2013
Meningococcal (MCV4-Menveo)	formaldehyde, amino acids, yeast extract, Franz complete medium, CY medium	August 2013
Meningococcal (MPSV4-Menomune)	thimerosal (multi-dose vial only), lactose, Mueller Hinton casein agar, Watson Scherp media, detergent, alcohol	April 2013
Meningococcal (MenB – Bexsero)	aluminum hydroxide, *E. coli*, histidine, sucrose, deoxycholate, kanomycin	2015
Meningococcal (MenB – Trumenba)	polysorbate 80, histodine, *E. coli*, fermentation growth media	October 2015
MMR (MMR-II)	Medium 199 (vitamins, amino acids, fetal bovine serum, sucrose, glutamate) , Minimum Essential Medium, phosphate, recombinant human albumin, neomycin, sorbitol, hydrolyzed gelatin, chick embryo cell culture, WI-38 human diploid lung fibroblasts	June 2014
MMRV (ProQuad)	sucrose, hydrolyzed gelatin, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium phosphate dibasic, neomycin, bovine calf serum, chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells	March 2014
Pneumococcal (PCV13 – Prevnar 13)	casamino acids, yeast, ammonium sulfate, Polysorbate 80, succinate buffer, aluminum phosphate, soy peptone broth	January 2014
Pneumococcal (PPSV-23 – Pneumovax)	phenol	May 2014
Polio (IPV – Ipol)	2-phenoxyethanol, formaldehyde, neomycin, streptomycin, polymyxin B, monkey kidney cells, Eagle MEM modified medium, calf serum protein, Medium 199	May 2013
Rabies (Imovax)	Human albumin, neomycin sulfate, phenol red indicator, MRC-5 human diploid cells, beta-propriolactone	April 2013
Rabies (RabAvert)	β-propiolactone, potassium glutamate, chicken protein, egg protein, neomycin, chlortetracycline, amphotericin B, human serum albumin, polygeline (processed bovine gelatin), sodium EDTA, bovine serum	March 2012
Rotavirus (RotaTeq)	sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, fetal bovine serum, vero cells *[DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq. PCV-1 and PCV-2 are not known to cause disease in humans.]*	June 2013
Rotavirus (Rotarix)	amino acids, dextran, sorbitol, sucrose, calcium carbonate, xanthan, Dulbecco's Modified Eagle Medium (potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red) *[Porcine circovirus type 1 (PCV-1) is present in Rotarix. PCV-1 is not known to cause disease in humans.]*	May 2014
Smallpox (Vaccinia – ACAM2000)	human serum albumin, mannitol, neomycin, glycerin, polymyxin B, phenol, Vero cells, HEPES	September 2009

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Appendix B

Vaccine	Contains	Source: Manufacturer's P.I. Dated
Td (Decavac)	aluminum potassium sulfate, peptone, formaldehyde, thimerosal, bovine muscle tissue (US sourced), Mueller and Miller medium, ammonium sulfate	March 2011
Td (Tenivac)	aluminum phosphate, formaldehyde, modified Mueller-Miller casamino acid medium without beef heart infusion, ammonium sulfate	April 2013
Td (Mass Biologics)	aluminum phosphate, formaldehyde, thimerosal (trace), ammonium phosphate, modified Mueller's media (containing bovine extracts)	February 2011
Tdap (Adacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol, ammonium sulfate, Stainer-Scholte medium, dimethyl-beta-cyclodextrin, modified Mueller's growth medium, Mueller-Miller casamino acid medium (without beef heart infusion)	March 2014
Tdap (Boostrix)	formaldehyde, glutaraldehyde, aluminum hydroxide, polysorbate 80 (Tween 80), Latham medium derived from bovine casein, Fenton medium containing a bovine extract, Stainer-Scholte liquid medium	February 2013
Typhoid (inactivated – Typhim Vi)	hexadecyltrimethylammonium bromide, formaldehyde, phenol, polydimethylsiloxane, disodium phosphate, monosodium phosphate, semi-synthetic medium	March 2014
Typhoid (oral – Ty21a)	yeast extract, casein, dextrose, galactose, sucrose, ascorbic acid, amino acids, lactose, magnesium stearate. gelatin	September 2013
Varicella (Varivax)	sucrose, phosphate, glutamate, gelatin, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, sodium phosphate monobasic, potassium chloride, EDTA, residual components of MRC-5 cells including DNA and protein, neomycin, fetal bovine serum, human diploid cell cultures (WI-38), embryonic guinea pig cell cultures, human embryonic lung cultures	March 2014
Yellow Fever (YF-Vax)	sorbitol, gelatin, egg protein	May 2013
Zoster (Shingles – Zostavax)	sucrose, hydrolyzed porcine gelatin, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, neomycin, potassium chloride, residual components of MRC-5 cells including DNA and protein, bovine calf serum	February 2014

A table listing vaccine excipients and media *by excipient* can be found in:

Grabenstein JD. *ImmunoFacts: Vaccines and Immunologic Drugs* – 2013 (38th revision). St Louis, MO: Wolters Kluwer Health, 2012.

B

242 – Pentacel®

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Pentacel safely and effectively. See full prescribing information for Pentacel.

Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine
Suspension for Intramuscular Injection
Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES----------

----------INDICATIONS AND USAGE----------
- Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel vaccine is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to 5th birthday). (1)

----------DOSAGE AND ADMINISTRATION----------
- The four dose immunization series consists of a 0.5-mL intramuscular injection, after reconstitution, administered at 2, 4, 6 and 15-18 months of age. (2.1)
- Pentacel consists of a liquid vaccine component (DTaP-IPV component) and a lyophilized vaccine component (ActHIB vaccine). Reconstitute the ActHIB vaccine component with the DTaP-IPV component immediately before administration.(2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Suspension for injection (0.5-mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials. (3)

----------CONTRAINDICATIONS----------
- Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel vaccine, any ingredient of Pentacel vaccine, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or *H. influenzae* type b vaccine. (4.1)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)
- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

----------WARNINGS AND PRECAUTIONS----------
- Carefully consider benefits and risks before administering Pentacel to persons with a history of:
  - fever ≥40.5°C (≥105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
  - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel. (5.3)
- For infants and children with a history of previous seizures, an antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with Pentacel and for the next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.7)

----------ADVERSE REACTIONS----------
- Rates of adverse reactions varied by dose number. Systemic reactions that occurred in >50% of participants following any dose included fussiness/irritability and inconsolable crying. Fever ≥38.0°C occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in >30% of participants following any dose included tenderness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

----------DRUG INTERACTIONS----------
- Do not mix Pentacel or any of its components with any other vaccine or diluent. (7.1)
- Immunosuppressive therapies may reduce the immune response to Pentacel. (7.2)
- Urine antigen detection may not have definitive diagnostic value in suspected *H influenzae* type b disease within one week following Pentacel. (7.3)

See 17 for PATIENT COUNSELING INFORMATION
Revised: [10/2013]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Pentacel® is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel vaccine is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to fifth birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Immunization Series

Pentacel vaccine is to be administered as a 4 dose series at 2, 4, 6 and 15-18 months of age. The first dose may be given as early as 6 weeks of age. Four doses of Pentacel vaccine constitute a primary immunization course against pertussis. Three doses of Pentacel vaccine constitute a primary immunization course against diphtheria, tetanus, *H influenzae* type b invasive disease, and poliomyelitis; the fourth dose is a booster for diphtheria, tetanus, *H influenzae* type b invasive disease, and poliomyelitis immunizations. [See *14 Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)*.]

Mixed Sequences of Pentacel Vaccine and DTaP Vaccine

While Pentacel and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed [DTaP], Sanofi Pasteur Limited) vaccines contain the same pertussis antigens, manufactured by the same process, Pentacel vaccine contains twice the amount of detoxified pertussis toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL vaccine. Pentacel vaccine may be used to complete the first 4 doses of the 5-dose DTaP series in infants and children who have received 1 or more doses of DAPTACEL vaccine and are also scheduled to receive the other antigens of Pentacel vaccine. However, data are not available on the safety and immunogenicity of such mixed sequences of Pentacel vaccine and DAPTACEL vaccine for successive doses of the primary DTaP series. Children who have completed a 4-dose series with Pentacel vaccine should receive a fifth dose of DTaP vaccine using DAPTACEL at 4-6 years of age. (1)

Data are not available on the safety and effectiveness of using mixed sequences of Pentacel vaccine and DTaP vaccine from different manufacturers.

Mixed Sequences of Pentacel Vaccine and IPV Vaccine

Pentacel vaccine may be used in infants and children who have received 1 or more doses of another licensed IPV vaccine and are scheduled to receive the antigens of Pentacel vaccine. However, data are not available on the safety and immunogenicity of Pentacel vaccine in such infants and children.

The Advisory Committee on Immunization Practices (ACIP) recommends that the final dose in the 4-dose IPV series be administered at age ≥4 years. (2) When Pentacel vaccine is administered at ages 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine should be administered at age 4-6 years, resulting in a 5-dose IPV series. (2)

Mixed Sequences of Pentacel Vaccine and Haemophilus b Conjugate Vaccine

Pentacel vaccine may be used to complete the vaccination series in infants and children previously vaccinated with one or more doses of Haemophilus b Conjugate Vaccine (either separately administered or as part of another combination vaccine), who are also scheduled to receive the other antigens of Pentacel vaccine. However, data are not available on the safety and immunogenicity of Pentacel vaccine in such infants and children. If different brands of Haemophilus b Conjugate Vaccines are administered to complete the series, three primary immunizing doses are needed, followed by a booster dose.

2.2 Administration

The package contains a vial of the DTaP-IPV component and a vial of lyophilized ActHIB vaccine component.

After removing the "flip-off" caps, cleanse the DTaP-IPV and ActHIB vial stoppers with a suitable germicide. Do not remove the vial stoppers or metal seals holding them in place. Just before use, thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire liquid content and inject into the vial of the lyophilized ActHIB vaccine component. Gently swirl the vial now containing Pentacel vaccine until a cloudy, uniform, white to off-white (yellow tinge) suspension results.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, Pentacel vaccine should not be administered.

Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL dose of Pentacel vaccine intramuscularly. Use a separate sterile needle and syringe for each injection. Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Pentacel vaccine should be used immediately after reconstitution. Refer to Figures 1, 2, 3, 4 and 5.

Pentacel Vaccine: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV Component

Figure 1
Gently shake the vial of DTaP-IPV component.

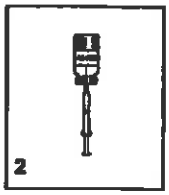

Figure 2
Withdraw the entire liquid content.

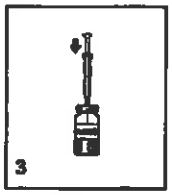

Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

Figure 4
Swirl vial gently.

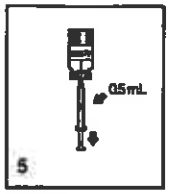

Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly. Pentacel vaccine should be used immediately after reconstitution.

In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously or subcutaneously.

Pentacel vaccine should not be mixed in the same syringe with other parenteral products.

3 DOSAGE FORMS AND STRENGTHS

Pentacel vaccine is a suspension for injection (0.5-mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials. [See *Dosage and Administration (2.2)* and *How Supplied/Storage and Handling (16)*.]

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel vaccine or any other diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, inactivated poliovirus vaccine or *H influenzae* type b vaccine, or any ingredient of this vaccine is a contraindication to administration of Pentacel vaccine. [See *Description (11)*.]

4.2 Encephalopathy

Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including Pentacel vaccine.

4.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a contraindication to administration of any pertussis-containing vaccine including Pentacel vaccine. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Adverse Reactions Following Prior Pertussis Vaccination

If any of the following events occur within the specified period after administration of a pertussis vaccine, the decision to administer Pentacel vaccine should be based on careful consideration of potential benefits and possible risks.

- Temperature of ≥40.5°C (≥105°F) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode (HHE)) within 48 hours.
- Persistent, inconsolable crying lasting ≥3 hours within 48 hours.
- Seizures with or without fever within 3 days.

5.3 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (3) If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel vaccine.

5.4 Infants and Children with a History of Previous Seizures

For infants or children with a history of previous seizures, an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing acellular pertussis antigens (including Pentacel vaccine) and for the following 24 hours, to reduce the possibility of post-vaccination fever.

5.5 Limitations of Vaccine Effectiveness

Vaccination with Pentacel vaccine may not protect all individuals.

5.6 Altered Immunocompetence

If Pentacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See *Drug Interactions (7.2)*.]

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS

6.1 Data from Clinical Studies

Rates of adverse reactions varied by dose number. The most frequent (>50% of participants) systemic reactions following any dose were fussiness/irritability and inconsolable crying. The most frequent (>30% of participants) injection site reactions following any dose were tenderness and increased circumference of the injected arm.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

The safety of Pentacel vaccine was evaluated in four clinical studies in which a total of 5,960 participants received at least one dose of Pentacel vaccine. In three of the studies, conducted in the US, a total of 4,198 participants were enrolled to receive four consecutive doses of Pentacel vaccine. In the fourth study, conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel vaccine received a fourth dose. The vaccination schedules of Pentacel vaccine, Control vaccines, and concomitantly administered vaccines used in these studies are provided in Table 1.

Across the four studies, 50.8% of participants were female. Among participants in the three US studies, 64.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and 9.5% were of other racial/ethnic groups. In the two controlled studies, the racial/ethnic distribution of participants who received Pentacel and Control vaccines was similar. In the Canadian fourth dose study, 86.0% of participants were Caucasian, 1.9% were Black, 0.8% were Hispanic, 4.3% were Asian, 2.0% were East Indian, 0.5% were Native Indian, and 4.5% were of other racial/ethnic groups.

Table 1: Clinical Safety Studies of Pentacel Vaccine: Vaccination Schedules

Study	Pentacel	Control Vaccines	Concomitantly Administered Vaccines
494-01	2, 4, 6, and 15 months	HCPDT + POLIOVAX + ActHIB at 2, 4, 6, and 15 months	7-valent pneumococcal conjugate vaccine* (PCV7) at 2, 4, and 6 months in a subset of participants† Hepatitis B vaccine at 2 and 6 months‡
P3T06	2, 4, 6, and 15-16 months	DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months; and DAPTACEL + ActHIB at 15-16 months	PCV7* at 2, 4, and 6 months Hepatitis B vaccine at 2 and 6 months‡
494-03	2, 4, 6, and 15-16 months	None	PCV7* at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants Hepatitis B vaccine at 2 and 6 months (if a dose was previously administered)‡; or at 2, 4, and 6 months (if no previous dose) Measles, mumps, rubella vaccine§ (MMR) and varicella§ vaccine at 12 or 15 months in random subsets of participants
5A9906	15-16 months**	None	None

HCPDT: non-US licensed DTaP vaccine that is identical to the DTaP component of Pentacel vaccine.
POLIOVAX: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited.
IPOL: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur SA.

* PCV7 manufactured by Wyeth Laboratories.
† PCV7 was introduced after the study was initiated, and thus, administered concomitantly with Pentacel vaccine in a subset of participants.
‡ The first dose of hepatitis B vaccine (manufacturer not specified) was administered prior to study initiation, from birth to 21 days of age. Subsequent doses were with hepatitis B vaccine manufactured by Merck and Co.
§ MMR and varicella vaccines were both manufactured by Merck and Co.
** Study participants previously had received three doses of Pentacel vaccine by 6 months of age.

Solicited Adverse Reactions

The incidence and severity of selected solicited injection site and systemic adverse reactions that occurred within 3 days following each dose of Pentacel or Control vaccines in Study P3T06 is shown in Table 2. Information on these reactions was recorded daily by parents or guardians on diary cards. In Table 2, injection site reactions are reported for the Pentacel vaccine and DAPTACEL vaccine injection sites.

Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by Severity Occurring within 0-3 days of Pentacel Vaccine or Control Vaccines in Study P3T06

	Pentacel Vaccine				DAPTACEL Vaccine			
Injection Site Reactions	Dose 1 N = 465-467 %	Dose 2 N = 451 %	Dose 3 N = 438-440 %	Dose 4 N = 387-396 %	Dose 1 N = 1,400-1,404 %	Dose 2 N = 1,358-1,359 %	Dose 3 N = 1,311-1,312 %	Dose 4 N = 376-380 %
Redness								
>5 mm	7.1	8.4	8.7	17.3	6.2	7.1	9.6	16.4
>25 mm	2.8	1.8	1.8	9.2	1.0	0.6	1.9	7.9
>50 mm	0.6	0.2	0.0	2.3	0.4	0.1	0.0	2.4
Swelling								
>5 mm	7.5	7.3	5.0	9.7	4.0	4.0	6.5	10.3
>25 mm	3.0	2.0	1.6	3.8	1.6	0.7	1.1	4.0
>50 mm	0.9	0.0	0.0	0.8	0.4	0.1	0.1	1.3
Tenderness*								
Any	47.5	39.2	42.7	56.1	48.8	38.2	40.9	51.1
Moderate or Severe	19.6	10.6	11.6	16.7	20.7	12.2	12.3	15.8
Severe	5.4	1.6	1.4	3.3	4.1	2.3	1.7	2.4
Increase in Arm Circumference								
>5 mm	—	—	—	33.6	—	—	—	30.6
>20 mm				4.7				6.9
>40 mm				0.5				0.8

	Pentacel Vaccine				DAPTACEL + IPOL + ActHIB Vaccines			DAPTACEL + ActHIB Vaccines
Systemic Reactions	Dose 1 N = 466-467 %	Dose 2 N = 451-452 %	Dose 3 N = 435-440 %	Dose 4 N = 389-398 %	Dose 1 N = 1,390-1,406 %	Dose 2 N = 1,346-1,360 %	Dose 3 N = 1,301-1,312 %	Dose 4 N = 379-381 %
Fever†‡								
≥38.0°C	5.8	10.9	16.3	13.4	9.3	16.1	15.8	8.7
>38.5°C	1.3	2.4	4.4	5.1	1.8	4.3	5.1	3.2
>39.5°C	0.4	0.0	0.7	0.3	0.1	0.4	0.3	0.8
Decreased Activity/ Lethargy§								
Any	45.8	32.7	32.5	24.1	51.1	37.4	33.2	24.1
Moderate or Severe	22.9	12.4	12.7	9.8	24.3	15.8	12.7	9.2
Severe	2.1	0.7	0.2	2.5	1.2	1.4	0.8	0.3
Inconsolable Crying								
Any	59.3	49.8	47.3	35.9	58.6	51.4	47.9	36.2
≥1 hour	19.7	10.8	13.6	11.8	16.4	16.0	12.2	10.5
>3 hours	1.9	0.9	1.1	2.3	2.2	3.4	1.4	1.8
Fussiness/ Irritability								
Any	76.9	71.2	68.0	53.5	75.8	70.7	67.1	53.8
≥1 hour	34.5	27.0	26.4	23.8	33.3	30.5	28.2	19.4
>3 hours	4.3	4.0	5.0	5.3	5.8	5.5	4.3	4.5

* Any: Mild, Moderate or Severe; Mild: subject whimpers when site is touched; Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.
† Fever is based upon actual temperatures recorded with no adjustments to the measurement route.
‡ Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 46.0%, 53.0%, 1.0%, and 0% respectively, for Pentacel vaccine and 44.8%, 54.0%, 1.0%, and 0.1%, respectively, for DAPTACEL + IPOL + ActHIB vaccines. Following Dose 4, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 62.7%, 34.4%, 2.4% and 0.5%, respectively, for Pentacel vaccine, and 61.1%, 36.6%, 1.7% and 0.5%, respectively, for DAPTACEL + ActHIB vaccines.
§ Moderate: Interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

Hypotonic Hyporesponsive Episodes

In Study P3T06, the diary cards included questions pertaining to HHEs. In Studies 494-01, 494-03, and 5A9906, a question about the occurrence of fainting or change in mental status was asked during post-vaccination phone calls. Across these 4 studies, no HHEs, as defined in a report of a US Public Health Service workshop (4) were reported among participants who received Pentacel vaccine (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB vaccines (N = 1,032) or separately administered DAPTACEL + IPOL + ActHIB vaccines (N = 1,455). Hypotonia not fulfilling HHE criteria within 7 days following vaccination was reported in 4 participants after the administration of Pentacel vaccine (1 on the same day as the 1st dose; 3 on the same day as the 3rd dose) and in 1 participant after the administration of DAPTACEL + IPOL + ActHIB vaccines (4 days following the 1st dose).

Seizures

Across Studies 494-01, 494-03, 5A9906 and P3T06, a total of 8 participants experienced a seizure within 7 days following either Pentacel vaccine (4 participants; N = 4,197 for at least one of Doses 1-3; N = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB vaccines (3 participants; N = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4), separately administered DAPTACEL + IPOL + ActHIB vaccines (1 participant; N = 1,455 for at least one of Doses 1-3), or separately administered DAPTACEL + ActHIB vaccines (0 participants; N = 418 for Dose 4). Among the four participants who experienced a seizure within 7 days following Pentacel vaccine, one participant in Study 494-01 had an afebrile seizure 6 days after the first dose, one participant in Study 494-01 had a possible seizure the same day as the third dose, and two participants in Study 5A9906 had a febrile seizure 2 and 4 days, respectively, after the fourth dose. Among the four participants who experienced a seizure within 7 days following Control vaccines, one participant had an afebrile seizure the same day as the first dose of DAPTACEL + IPOL + ActHIB vaccines, one participant had an afebrile seizure the same day as the second dose of HCPDT + POLIOVAX + ActHIB vaccines, and two participants had a febrile seizure 6 and 7 days, respectively, after the fourth dose of HCPDT + POLIOVAX + ActHIB vaccines.

Serious Adverse Events

In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of 484 (3.9%) participants who received Pentacel vaccine and 60 of 1,455 (3.4%) participants who received DAPTACEL + IPOL + ActHIB vaccines experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel vaccine and 4 of 418 (1.0%) participants who received DAPTACEL + ActHIB vaccines experienced a serious adverse event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 23 of 2,506 (0.9%) participants who received Pentacel vaccine and 11 of 1,032 (1.1%) participants who received HCPDT + POLIOVAX + ActHIB vaccines experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants who received Pentacel vaccine and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX + ActHIB vaccines experienced a serious adverse event.

Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03, 5A9906 and P3T06, within 30 days following Dose 4 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia.

Across Studies 494-01, 494-03, 5A9906 and P3T06, two cases of encephalopathy were reported, both in participants who had received Pentacel vaccine (N = 5,979). One case occurred 30 days post-vaccination and was secondary to cardiac arrest following cardiac surgery. One infant who had onset of neurologic symptoms 8 days post-vaccination was subsequently found to have structural cerebral abnormalities and was diagnosed with congenital encephalopathy.

A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9906 and P3T06: 4 in children who had received Pentacel vaccine (N = 5,979) and one in a participant who had received DAPTACEL + IPOL + ActHIB vaccines (N = 1,455). There were no deaths reported in children who received HCPDT + POLIOVAX + ActHIB vaccines (N = 1,032). Causes of death among children who received Pentacel vaccine were asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (6, 23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died secondary to aspiration 222 days following DAPTACEL + IPOL + ActHIB vaccines.

6.2 Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of Pentacel vaccine worldwide, since 1997. Between 1997 and 2007, Pentacel vaccine was primarily used in Canada. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Pentacel vaccine.

- ***Cardiac disorders***
  Cyanosis
- ***Gastrointestinal disorders***
  Vomiting, diarrhea
- ***General disorders and administration site conditions***
  Injection site reactions (including inflammation, mass, abscess and sterile abscess), extensive swelling of the injected limb (including swelling that involved adjacent joints), vaccination failure/therapeutic response decreased (invasive *H influenzae* type b disease)
- ***Immune system disorders***
  Anaphylaxis/anaphylactic reaction, hypersensitivity (such as rash and urticaria)
- ***Infections and infestations***
  Meningitis, rhinitis, viral infection
- ***Metabolism and nutrition disorders***
  Decreased appetite
- ***Nervous system disorders***
  Somnolence, HHE, depressed level of consciousness
- ***Psychiatric disorders***
  Screaming

- ***Respiratory, thoracic and mediastinal disorders***
  Apnea, cough
- ***Skin and subcutaneous tissue disorders***
  Erythema, skin discoloration
- ***Vascular disorders***
  Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

In clinical trials, Pentacel vaccine was administered concomitantly with one or more of the following US licensed vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and varicella vaccines. [See *Adverse Reactions (6)* and *Clinical Studies (14)*.] When Pentacel vaccine is given at the same time as another injectable vaccine(s), the vaccine(s) should be administered with different syringes and at different injection sites.

7.2 Immunosuppressive Treatments

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to Pentacel vaccine. [See *Warnings and Precautions (5.6)*.]

7.3 Drug/Laboratory Test Interactions

Antigenuria has been detected in some instances following receipt of ActHIB vaccine. Urine antigen detection may not have definite diagnostic value in suspected *H influenzae* type b disease within one week following receipt of Pentacel vaccine. (5)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Pentacel vaccine. It is also not known whether Pentacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

8.4 Pediatric Use

The safety and effectiveness of Pentacel vaccine was established in the age group 6 weeks through 18 months on the basis of clinical studies. [See *Adverse Reactions (6.1)* and *Clinical Studies (14)*.] The safety and effectiveness of Pentacel vaccine in the age group 19 months through 4 years is supported by evidence in children 6 weeks through 18 months. The safety and effectiveness of Pentacel vaccine in infants less than 6 weeks of age and in children 5 to 16 years of age have not been established.

11 DESCRIPTION

Pentacel vaccine consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (DTaP-IPV) component and an ActHIB® vaccine component combined through reconstitution for intramuscular injection. ActHIB vaccine (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]), consists of *H influenzae* type b capsular polysaccharide (polyribosyl ribitol-phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T). The DTaP-IPV component is supplied as a sterile liquid used to reconstitute the lyophilized ActHIB vaccine component to form Pentacel vaccine. Pentacel vaccine is a uniform, cloudy, white to off-white (yellow tinge) suspension.

Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], inactivated polioviruses [40 D antigen units (DU) Type 1 (Mahoney), 8 DU Type 2 (MEF-1), 32 DU Type 3 (Saukett)] and 10 mcg PRP of *H influenzae* type b covalently bound to 24 mcg of tetanus toxoid (PRP-T).

Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), 42.5 mg sucrose, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative), <4 pg of neomycin and <4 pg polymyxin B sulfate.

Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (6) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and diafiltered.

Clostridium tetani is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (7) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The acellular pertussis vaccine antigens are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (8) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

Poliovirus Type 1, Type 2 and Type 3 are each grown in separate cultures of MRC-5 cells, a line of normal human diploid cells, by the microcarrier method. (9) (10) The cells are grown in CMRL (Connaught Medical Research Laboratories) 1969 medium, supplemented with calf serum. For viral growth, the culture medium is replaced by Medium 199, without calf serum. After clarification and filtration, the viral suspensions are concentrated by ultrafiltration, and purified by liquid chromatography steps. The monovalent viral suspensions are inactivated with formaldehyde. Monovalent concentrates of each inactivated poliovirus are combined to produce a trivalent poliovirus concentrate.

The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the DTaP-IPV component is diluted to its final concentration. The DTaP-IPV component does not contain a preservative.

Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig potency test. The potency of the acellular pertussis antigens is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA). The immunogenicity of the inactivated polioviruses is evaluated by the antibody response in monkeys measured by virus neutralization.

PRP, a high molecular weight polymer, is prepared from the *Haemophilus influenzae* type b strain 1482 grown in a semi-synthetic medium. (11) The tetanus toxoid for conjugation to PRP is prepared by ammonium sulfate purification, and formalin inactivation of the toxin from cultures of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (12) The toxoid is filter sterilized prior to the conjugation process. The ActHIB vaccine component does not contain a preservative. Potency of the ActHIB vaccine component is specified on each lot by limits on the content of PRP polysaccharide and protein per dose and the proportion of polysaccharide and protein that is characterized as high molecular weight conjugate.

The vial stoppers for the DTaP-IPV and ActHIB vaccine components of Pentacel vaccine are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (13) Levels of 1.0 IU/mL have been associated with long-term protection. (14)

Tetanus

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (13) (15) A tetanus antitoxoid level ≥0.1 IU/mL as measured by the ELISA used in clinical studies of Pentacel vaccine is considered protective.

Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

Poliomyelitis

Polioviruses, of which there are three serotypes (Types 1, 2, and 3) are enteroviruses. The presence of poliovirus type-specific neutralizing antibodies has been correlated with protection against poliomyelitis. (16)

Invasive Disease Due to *H influenzae* Type b

H influenzae type b can cause invasive disease such as meningitis and sepsis. Anti-PRP antibody has been shown to correlate with protection against invasive disease due to *H influenzae* type b.

Based on data from passive antibody studies (17) and an efficacy study with *H influenzae* type b polysaccharide vaccine in Finland, (18) a post-vaccination anti-PRP level of 0.15 mcg/mL has been accepted as a minimal protective level. Data from an efficacy study with *H influenzae* type b polysaccharide vaccine in Finland indicate that a level >1.0 mcg/mL 3 weeks after vaccination predicts protection through a subsequent one-year period. (19) (20) These levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB vaccine component of Pentacel vaccine.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Pentacel vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

The efficacy of Pentacel vaccine is based on the immunogenicity of the individual antigens compared to separately administered vaccines. Serological correlates of protection exist for diphtheria, tetanus, poliomyelitis, and invasive disease due to *H influenzae* type b. [See *Clinical Pharmacology (12.1)*.] The efficacy against pertussis, for which there is no well established serological correlate of protection, was based, in part, on a comparison of pertussis immune responses following Pentacel vaccine in US children to responses following DAPTACEL vaccine (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) manufactured by Sanofi Pasteur Limited) in an efficacy study conducted in Sweden (Sweden I Efficacy Trial). While Pentacel and DAPTACEL vaccines contain the same pertussis antigens, manufactured by the same process, Pentacel vaccine contains twice as much detoxified PT and four times as much FHA as DAPTACEL vaccine.

Immune responses to Pentacel vaccine were evaluated in four US studies: Studies 494-01, P3T06, 494-03, and M5A10. The vaccination schedules of Pentacel vaccine, Control vaccines, and concomitantly administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in Table 1. [See *Adverse Reactions (6.1)*.] In Study M5A10, participants were randomized to receive Pentacel vaccine or separately administered DAPTACEL, IPOL, and ActHIB vaccines at 2, 4, and 6 months of age. 7-valent pneumococcal conjugate vaccine (PCV7, Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age, and Hepatitis B vaccine (Merck and Co. or GlaxoSmithKline Biologicals) at 2 and 6 months of age, were administered concomitantly with Pentacel vaccine or Control vaccines.

14.1 Diphtheria

The proportions of participants achieving diphtheria antitoxin seroprotective levels one month following three and four doses of Pentacel vaccine or DAPTACEL vaccine in Study P3T06 are provided in Table 3.

14.2 Tetanus

The proportions of participants achieving tetanus antitoxoid seroprotective levels one month following three and four doses of Pentacel vaccine or DAPTACEL vaccine in Study P3T06 are provided in Table 3.

Table 3: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month Following Dose 3 and Dose 4 of Pentacel Vaccine or DAPTACEL + IPOL + ActHIB Vaccines in US Children Vaccinated at 2, 4, 6, and 15-16 Months of Age

Post-Dose 3	Pentacel Vaccine	DAPTACEL + IPOL + ActHIB Vaccines
	N = 331-345	N = 1,037-1,059
Diphtheria Antitoxin		
% ≥0.01 IU/mL*	100.0%	100.0%
% ≥0.10 IU/mL†	98.8%	98.5%
Tetanus Antitoxoid		
% ≥0.10 IU/mL†	99.7%	100.0%
Post-Dose 4	**N = 341-352**	**N = 328-334**
Diphtheria Antitoxin		
% ≥0.10 IU/mL*	100.0%	100.0%
% ≥1.0 IU/mL†	96.5%	95.7%
Tetanus Antitoxoid		
% ≥0.10 IU/mL*	100.0%	100.0%
% ≥1.0 IU/mL†‡	82.0%	98.4%

Per Protocol Immunogenicity population.

* Seroprotection rate following Pentacel vaccine is not inferior to DAPTACEL vaccine (upper limit of 90% CI of the difference DAPTACEL – Pentacel is <10%).

† Non-inferiority criteria were not pre-specified.

‡ With the ELISA used in this study, a tetanus antitoxoid level of 1.0 IU/mL is 10 times the protective level.

14.3 Pertussis

In a clinical pertussis vaccine efficacy study conducted in Sweden during 1992-1995 (Sweden I Efficacy Trial), 2,587 infants received DAPTACEL vaccine and 2,574 infants received a non-US licensed DT vaccine as placebo at 2, 4, and 6 months of age. (1) The mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of DAPTACEL vaccine against pertussis after 3 doses of vaccine using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1%, 88.6%). The protective efficacy of DAPTACEL vaccine against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6%, 82.2%). Protection against pertussis by DAPTACEL vaccine was sustained for the 2-year follow-up period.

Based on comparisons of the immune responses to DAPTACEL vaccine in US infants (Post-Dose 3) and Canadian children (Post-Dose 4) relative to infants who participated in the Sweden I Efficacy Trial, it was concluded that 4 doses of DAPTACEL vaccine were needed for primary immunization against pertussis in US children. (1)

In a serology bridging analysis, immune responses to FHA, PRN and FIM in a subset of infants who received three doses of DAPTACEL vaccine in the Sweden I Efficacy Trial were compared to the Post-Dose 3 and Post-Dose 4 responses in a subset of US children from Study 494-01 who received Pentacel vaccine (Table 4). Available stored sera from infants who received DAPTACEL vaccine in the Sweden I Efficacy Trial and sera from children who received PCV7 concomitantly with the first three doses of Pentacel vaccine in Study 494-01 (Table 1) were assayed in parallel. Data on levels of antibody to PT using an adequately specific assay were not available for this serology bridging analysis.

Geometric mean antibody concentrations (GMCs) and seroconversion rates for antibodies to FHA, PRN and FIM one month following Dose 3 of DAPTACEL vaccine in the subset of infants from the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel vaccine in a subset of infants from US Study 494-01 are presented in Table 4. Seroconversion was defined as 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). For anti-FHA and anti-FIM, the non-inferiority criteria were met for seroconversion rates, and for anti-FHA, anti-PRN, and anti-FIM, the non-inferiority criteria were met for GMCs, following Dose 4 of Pentacel vaccine relative to Dose 3 of DAPTACEL vaccine. The non-inferiority criterion for anti-PRN seroconversion following Dose 4 of Pentacel vaccine relative to Dose 3 of DAPTACEL vaccine was not met [upper limit of 95% CI for difference in rate (DAPTACEL minus Pentacel) = 13.24%]. Whether the lower anti-PRN seroconversion rate following Dose 4 of Pentacel vaccine in US children relative to Dose 3 of DAPTACEL vaccine in Swedish infants correlates with diminished efficacy of Pentacel vaccine against pertussis is unknown.

Table 4: FHA, PRN and FIM Antibody Responses One Month Following Dose 3 of DAPTACEL Vaccine in a Subset of Infants Vaccinated at 2, 4, and 6 Months of Age in the Sweden I Efficacy Trial and One Month Following Dose 3 and Dose 4 of Pentacel Vaccine in a Subset of Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in US Study 494-01

	Post-Dose 3 DAPTACEL Vaccine Sweden I Efficacy Trial N = 80	Post-Dose 3 Pentacel Vaccine* US Study 494-01 N = 730-895	Post-Dose 4 Pentacel Vaccine† US Study 494-01 N = 807-854
Anti-FHA % achieving 4-fold rise‡ GMC (EU/mL)	68.8 40.70	79.8 71.46	91.7§ 129.85§
Anti-PRN % achieving 4-fold rise‡ GMC (EU/mL)	98.8 111.26	74.4 38.11	89.2** 90.82§
Anti-FIM % achieving 4-fold rise‡ GMC (EU/mL)	86.3 339.31	86.5 265.02	91.5§ 506.57§

Analyzed sera were from subsets of the Per Protocol immunogenicity populations in each study. Data on anti-PT levels using an adequately specific assay were not available.

* Non-inferiority criteria were not pre-specified for the comparisons of immune responses to Pentacel vaccine Post-Dose 3 vs. DAPTACEL vaccine Post-Dose 3.

† Pre-specified non-inferiority analyses compared immune responses to Pentacel vaccine Post-Dose 4 vs. DAPTACEL vaccine Post-Dose 3.

‡ Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

§ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine is not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) <10% and upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5].

** Non-inferiority criterion is not met for percent achieving 4-fold rise in anti-PRN Post-Dose 4 Pentacel vaccine relative to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) = 13.24%, exceeds the non-inferiority criterion of <10%].

In a separate study, Study P3T06, US infants were randomized to receive either Pentacel vaccine or DAPTACEL + IPOL + ActHIB vaccines at 2, 4, 6, and 15-16 months of age (Table 1). The pertussis immune responses (GMCs and seroconversion rates) one month following the third and fourth doses were compared between the two vaccine groups (Table 5). Seroconversion was defined as a 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post Dose 4/Pre-Dose 1). Data on anti-PT responses obtained from an adequately specific assay were available on only a non-random subset of study participants. The subset of study participants was representative of all study participants with regard to Pre Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to FHA, PRN and FIM. For each of the pertussis antigens, non-inferiority criteria were met for seroconversion rates and GMCs following Dose 3 of Pentacel vaccine relative to Dose 3 of DAPTACEL vaccine. Following Dose 4 of Pentacel vaccine relative to Dose 4 of DAPTACEL vaccine, non-inferiority criteria were met for all comparisons except for anti-PRN GMCs [upper limit of 90% CI for ratio of GMCs (DAPTACEL/Pentacel) = 2.25]. Whether the lower anti-PRN GMC following Dose 4 of Pentacel vaccine relative to Dose 4 of DAPTACEL vaccine in US children correlates with diminished efficacy of Pentacel vaccine against pertussis is unknown.

Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel Vaccine or DAPTACEL + IPOL + ActHIB Vaccines in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in Study P3T06

	Post-Dose 3 Pentacel Vaccine	Post-dose 3 DAPTACEL + IPOL + ActHIB Vaccines	Post-Dose 4 Pentacel Vaccine	Post-Dose 4 DAPTACEL + ActHIB Vaccines
	N = 143	N = 481-485	N = 113	N = 127-128
Anti-PT % achieving 4-fold rise* GMC (EU/mL)	95.8† 102.62†	87.3 61.88	93.8‡ 107.89‡	91.3 100.29
	N = 218-316	N = 714-1,016	N = 230-357	N = 237-347
Anti-FHA % achieving 4-fold rise* GMC (EU/mL)	81.9§ 73.68§	80.9 29.22	88.4** 107.94**	79.3 64.02
Anti-PRN % achieving 4-fold rise* GMC (EU/mL)	74.2§ 36.05§	75.4 43.25	92.7** 93.59††	98.3 186.07
Anti-FIM % achieving 4-fold rise* GMC (EU/mL)	91.7§ 268.15§	86.3 287.18	93.5** 553.39**	91.6 513.54

Per Protocol immunogenicity population for anti-FHA, anti-PRN, and anti-FIM.
Non-random subset of per Protocol immunogenicity population for anti-PT. See text for further information on the subset evaluated.

* Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

† Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

‡ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

§ Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

** Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

†† Non-inferiority criterion is not met for GMC Post-Dose 4 Pentacel vaccine relative to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) = 2.25, which exceeds the non-inferiority criterion of <1.5].

14.4 Poliomyelitis

In Study P3T06 (Table 1), in which infants were randomized to receive the first three doses of Pentacel vaccine or DAPTACEL + IPOL + ActHIB vaccines at 2, 4, and 6 months of age, one month following the third dose of study vaccines, ≥99.4% of participants in both groups (Pentacel: N = 338-350), (DAPTACEL + IPOL + ActHIB: N = 1,050-1,097) achieved neutralizing antibody levels of ≥1:8 for Poliovirus types 1, 2, and 3.

In Study 494-01 (Table 1), in which infants were randomized to receive Pentacel vaccine or HCPDT + POLIOVAX + ActHIB vaccines, GMTs (1/dil) of antibodies to Poliovirus types 1, 2, and 3 one month following Dose 4 of Pentacel vaccine (N = 851-857) were 2,304, 4,178, and 4,415, respectively, and one month following Dose 4 of POLIOVAX vaccine (N = 284-287) were 2,330, 2,840, and 3,300, respectively.

14.5 Invasive Disease due to *H Influenzae* Type b

Anti-PRP seroprotection rates and GMCs one month following Dose 3 of Pentacel vaccine or separately administered ActHIB vaccine in studies 494-01, P3T06, and M5A10 are presented in Table 6. In Study 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an anti-PRP level ≥1.0 mcg/mL and for anti-PRP GMCs following Pentacel vaccine compared with separately administered ActHIB vaccine. In each of Studies P3T06 and M5A10, the non inferiority criterion was met for the proportion of participants who achieved an anti-PRP level ≥1.0 mcg/mL following Pentacel vaccine compared with separately administered ActHIB vaccine. In Study M5A10, the non-inferiority criterion was met for anti-PRP GMCs following Pentacel vaccine compared with separately administered ActHIB vaccine.

Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of Pentacel Vaccine or Separate DTaP + IPV + ActHIB Vaccines Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and M5A10

	Study 494-01	
	Pentacel Vaccine N = 1,127	HCPDT + POLIOVAX + ActHIB Vaccines N = 401
% achieving anti-PRP ≥0.15 mcg/mL % achieving anti-PRP ≥1.0 mcg/mL Anti-PRP GMC (mcg/mL)	95.4* 79.1† 3.19‡	98.3 88.8 6.23
	Study P3T06	
	Pentacel Vaccine N = 385	DAPTACEL + IPOL + ActHIB Vaccines N = 1,128
% achieving anti-PRP ≥0.15 mcg/mL % achieving anti-PRP ≥1.0 mcg/mL Anti-PRP GMC (mcg/mL)	92.3* 72.1* 2.31§	93.3 70.8 2.29
	Study M5A10	
	Pentacel Vaccine N = 826	DAPTACEL + IPOL + ActHIB Vaccines N = 421
% achieving anti-PRP ≥0.15 mcg/mL % achieving anti-PRP ≥1.0 mcg/mL Anti-PRP GMC (mcg/mL)	93.8** 75.1** 2.52††	90.3 74.8 2.38

Per Protocol immunogenicity population for all studies.
IPV indicates Poliovirus Vaccine Inactivated.

* Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel) <10%].

† Non-inferiority criterion not met for percent achieving anti-PRP ≥1.0 mcg/mL following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel), 12.9%, exceeds the non-inferiority criterion <10%].
‡ Non-inferiority criterion not met for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel), 2.28, exceeds the non-inferiority criterion <1.5].
§ Non-inferiority criterion not pre-specified.
¶ Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 95% CI for difference in rates (ActHIB minus Pentacel) <10%].
†† GMC following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel) <1.5].

In Study 494-01, at 15 months of age prior to receipt of Dose 4 of study vaccines, 68.6% of Pentacel vaccine recipients (N = 829) and 80.8% of separately administered ActHIB vaccine recipients (N = 276) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 98.2% of Pentacel vaccine recipients (N = 874) and 99.0% of separately administered ActHIB vaccine recipients (N = 291) had an anti-PRP level ≥1.0 mcg/mL.

In Study P3T06, at 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of Pentacel vaccine recipients (N = 335) and 60.7% of separately administered ActHIB vaccine recipients (N = 323) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel vaccine recipients (N = 361) and 95.9% of separately administered ActHIB vaccine recipients (N = 340) had an anti-PRP level ≥1.0 mcg/mL.

14.6 Concomitantly Administered Vaccines

In Study P3T06, (Table 1) there was no evidence for reduced antibody responses to hepatitis B vaccine (percent of participants with anti-HBsAg ≥10 mIU/mL and GMCs) or PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL and GMCs to each serotype) administered concomitantly with Pentacel vaccine (N = 321-325) relative to these vaccines administered concomitantly with DAPTACEL + IPOL + ActHIB vaccines (N = 998-1,029). The immune responses to hepatitis B vaccine and PCV7 were evaluated one month following the third dose.

In Study 494-03, (Table 1) there was no evidence for interference in the immune response to the fourth dose of PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL and GMCs to each serotype) administered at 15 months of age concomitantly with Pentacel vaccine (N = 155) relative to this vaccine administered concomitantly with MMR and varicella vaccines (N = 158). There was no evidence for interference in the immune response to MMR and varicella vaccines (percent of participants with pre-specified seroresponse level) administered at 15 months of age concomitantly with Pentacel vaccine (N = 154) relative to these vaccines administered concomitantly with PCV7 (N = 144). The immune responses to MMR, varicella vaccine and the fourth dose of PCV7 were evaluated one month post-vaccination.

15 REFERENCES

1 DAPTACEL® [full prescribing information]. Toronto, ON: Sanofi Pasteur; 2011.
2 CDC. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. MMWR 2009;58:829-30.
3 Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington D.C.: National Academy Press. 1994. p. 67-117.
4 Braun MM. Report of a US Public Health Service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization. Pediatrics 1998;102(5)1-5.
5 Rothstein EP, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. Pediatr Infect Dis J 1991;10:311-4.
6 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings of an informal consultation on the World Health Organization requirements for diphtheria, tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda, MD. DHHS 91-1174. 1991. p. 7-11.
7 Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J Bacteriol 1954;67(3):271-7.
8 Stainer DW, et al. A simple chemically defined medium for the production of phase 1 Bordetella pertussis. J Gen Microbiol 1971;63:211-20.
9 van Wezel AL, et al. Inactivated poliovirus vaccine: current production methods and new developments. Rev Infect Dis 1984;6 (Suppl 2):S335-40.
10 Montagnon BJ et al. Industrial scale production of inactivated poliovirus vaccine prepared by culture of vero cells on microcarrier. Rev Infect Dis 1984;6 (Suppl 2):S341-4.
11 Chu CY, et al. Further studies on the immunogenicity of Haemophilus influenzae type b and pneumococcal type 6A polysaccharide-protein conjugates. Infect Immun 1983;40:245-56.
12 Mueller JH, et al. Production of diphtheria toxin of high potency (100 Lf) on a reproducible medium. J Immunol 1941;40:21-32.
13 Department of Health and Human Services, Food and Drug Administration. Biological products; bacterial vaccines and toxoids; implementation of efficacy review; proposed rule. Federal Register 1985;50(240):51002-117.
14 Vitek CR, Wharton M. Diphtheria toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W. B. Saunders; 2008. p. 139-66.
15 Wassilak SGF, et al. Tetanus toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W.B. Saunders; 2008. p. 805-39.
16 Sutter RW, et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. In: Williams JC, et al. eds. Combined vaccines and simultaneous administration. Current issues and perspectives. New York, NY: The New York Academy of Sciences. 1995:289-99.
17 Robbins JB, et al. Quantitative measurement of "natural" and immunization-induced Haemophilus influenzae type b capsular polysaccharide antibodies. Pediatr Res 1973;7:103-10.
18 Peltola H, et al. Haemophilus influenzae type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. Pediatrics 1977;60:730-7.
19 Keyhy H, et al. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1983;147:1100.
20 Anderson P. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1984;149:1034.

16 HOW SUPPLIED/STORAGE AND HANDLING

The vial stoppers for the DTaP-IPV and ActHIB vaccine components of Pentacel are not made with natural rubber latex.

5 Dose Package (NDC No. 49281-510-05) containing 5 vials of DTaP-IPV component (NDC No. 49281-560-05) to be used to reconstitute 5 single dose vials of lyophilized ActHIB vaccine component (NDC No. 49281-545-15).

Pentacel vaccine should be stored at 2° to 8°C (35° to 46°F). Do not freeze. Product which has been exposed to freezing should not be used. Do not use after expiration date shown on the label. Pentacel vaccine should be used immediately after reconstitution.

17 PATIENT COUNSELING INFORMATION

Before administration of Pentacel vaccine, health-care personnel should inform the parent or guardian of the benefits and risks of the vaccine and the importance of completing the immunization series unless a contraindication to further immunization exists.

The health-care provider should inform the parent or guardian about the potential for adverse reactions that have been temporally associated with Pentacel vaccine or other vaccines containing similar ingredients. The health-care provider should provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The parent or guardian should be instructed to report adverse reactions to their health-care provider.

Manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada
and
Sanofi Pasteur SA
Lyon France

Distributed by:
Sanofi Pasteur Inc.
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SANOFI PASTEUR

R4-1013 USA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ProQuad safely and effectively. See full prescribing information for ProQuad.

ProQuad®
Measles, Mumps, Rubella and Varicella Virus Vaccine Live
Suspension for subcutaneous injection
Initial U.S. Approval: 2005

----------INDICATIONS AND USAGE----------

ProQuad is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age. (1)

----------DOSAGE AND ADMINISTRATION----------

A 0.5-mL dose for subcutaneous injection only. (2.1)

- The first dose is usually administered at 12 to 15 months of age. (2.1)
- A second dose, if needed, is usually administered at 4 to 6 years of age. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Suspension for injection (0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using only accompanying sterile diluent. (2.2, 3)

----------CONTRAINDICATIONS----------

- History of anaphylactic reaction to neomycin or hypersensitivity to gelatin or any other component of the vaccine. (4.1)
- Primary or acquired immunodeficiency states. (4.2)
- Family history of congenital or hereditary immunodeficiency. (4.2)
- Immunosuppressive therapy. (4.2, 7.3)
- Active untreated tuberculosis or febrile illness (>101.3°F or >38.5°C). (4.3)
- Pregnancy. (4.4, 8.1, 17)

---------- WARNINGS AND PRECAUTIONS----------

- Administration of ProQuad (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with M-M-R® II and VARIVAX® administered separately. (5.1, 6.1, 6.3)
- Use caution when administering ProQuad to children with a history of cerebral injury or seizures or any other condition in which stress due to fever should be avoided. (5.2)
- Use caution when administering ProQuad to children with anaphylaxis or immediate hypersensitivity to eggs (5.3) or contact hypersensitivity to neomycin. (5.4)
- Use caution when administering ProQuad to children with thrombocytopenia. (5.5)
- Avoid close contact with high-risk individuals susceptible to varicella since transmission of varicella vaccine virus may occur between vaccinees and susceptible contacts. (5.8)
- Defer vaccination for at least 3 months following blood or plasma transfusions, or administration of immune globulins (IG). (5.9, 7.1)
- Avoid using salicylates for 6 weeks after vaccination with ProQuad. (6.1, 7.2, 17)
- Avoid pregnancy for 3 months following vaccination with measles, mumps, rubella, and/or varicella vaccines. (8.1, 17)

---------- ADVERSE REACTIONS ----------

- The most frequent vaccine-related adverse events reported in ≥5% of subjects vaccinated with ProQuad were:
  - injection-site reactions (pain/tenderness/soreness, erythema, and swelling)
  - fever
  - irritability. (6.1)
- Systemic vaccine-related adverse events that were reported at a significantly greater rate in recipients of ProQuad than in recipients of the component vaccines administered concomitantly were:
  - fever
  - measles-like rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS or exposure during pregnancy or within three months prior to conception, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------

- Tuberculin testing should be administered anytime before, simultaneously with, or at least 4 to 6 weeks after ProQuad. (7.4)
- ProQuad may be administered concomitantly with *Haemophilus influenzae* type b conjugate vaccine and/or hepatitis B vaccine at separate injection sites. (7.5)
- ProQuad may be administered concomitantly with pneumococcal 7-valent conjugate vaccine and/or hepatitis A vaccine (inactivated) at separate injection sites. (7.5)

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy: Do not administer ProQuad to females who are pregnant; the possible effects of the vaccine on fetal development are unknown at this time. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ProQuad® is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

FOR SUBCUTANEOUS ADMINISTRATION ONLY

Each 0.5-mL dose of ProQuad is administered subcutaneously.

The first dose is usually administered at 12 to 15 months of age but may be given anytime through 12 years of age.

If a second dose of measles, mumps, rubella, and varicella vaccine is needed, ProQuad may be used. This dose is usually administered at 4 to 6 years of age. At least 1 month should elapse between a dose of a measles-containing vaccine such as M-M-R® II (measles, mumps, and rubella virus vaccine live) and a dose of ProQuad. At least 3 months should elapse between a dose of varicella-containing vaccine and ProQuad.

2.2 Preparation for Administration

CAUTION: Preservatives, antiseptics, detergents, and other anti-viral substances may inactivate the vaccine. Use only sterile syringes that are free of preservatives, antiseptics, detergents, and other anti-viral substances for reconstitution and injection of ProQuad.

Withdraw the entire volume of the supplied diluent into a syringe. Use only the diluent supplied with the vaccine since it is free of preservatives or other anti-viral substances.

Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a white to pale yellow compact crystalline plug. ProQuad, when reconstituted, is a clear pale yellow to light pink liquid.

Withdraw the entire amount of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

TO MINIMIZE LOSS OF POTENCY, THE VACCINE SHOULD BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION. IF NOT USED IMMEDIATELY, THE RECONSTITUTED VACCINE MAY BE STORED AT ROOM TEMPERATURE, PROTECTED FROM LIGHT, FOR UP TO 30 MINUTES. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

2.3 Method of Administration

Inject the vaccine subcutaneously into the outer aspect of the deltoid region of the upper arm or into the higher anterolateral area of the thigh.

Use With Other Vaccines

Use different injection sites to administer each vaccine if other vaccines are administered concomitantly. *[See Drug Interactions (7.5).]*

3 DOSAGE FORMS AND STRENGTHS

ProQuad is a suspension for injection supplied as a 0.5-mL single dose vial of lyophilized vaccine to be reconstituted using the sterile diluent supplied *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer ProQuad to individuals with a history of anaphylactic reactions to neomycin. If vaccination with ProQuad is medically necessary for such individuals, they are advised to consult an allergist or immunologist and should receive ProQuad only in settings where anaphylactic reactions can be appropriately managed.

Do not administer ProQuad to individuals with a history of hypersensitivity to gelatin or any other component of the vaccine or following previous vaccination with ProQuad, VARIVAX® (varicella virus vaccine live), or any measles-, mumps-, or rubella-containing vaccine *[see Description (11) and Warnings and Precautions (5) for exceptions]*.

4.2 Immunosuppression

Do not administer ProQuad to individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or to individuals on immunosuppressive therapy (including high-dos stemic corticosteroids) *[see Drug Interactions (7.3)]*. Vaccination with a live, attenuated vaccine, such as varicella, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive drugs. ProQuad may be used by individuals who are receiving topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis or in patients who are receiving corticosteroids as replacement therapy, *e.g.*, for Addison's disease.

Do not administer ProQuad to individuals with primary and acquired immunodeficiency states, including AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis, pneumonitis, and death as a direct consequence of disseminated measles vaccine virus infection have been reported in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In addition, disseminated varicella vaccine virus infection has been reported in children with underlying immunodeficiency disorders who were inadvertently vaccinated with a varicella-containing vaccine {1}.

Do not administer ProQuad to individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

4.3 Concurrent Illness

Do not administer ProQuad to individuals with active untreated tuberculosis or to individuals with an active febrile illness with fever >101.3°F (>38.5°C).

4.4 Pregnancy

Do not administer ProQuad to individuals who are pregnant; the possible effects of the vaccine on fetal development are unknown at this time *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Fever and Febrile Seizures

Administration of ProQuad (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with dose 1 of both M-M-R II and VARIVAX administered separately *[see Adverse Reactions (6.3)]*.

5.2 History of Cerebral Injury or Seizures

Exercise caution when administering ProQuad to persons with a history of cerebral injury, individual or family history of convulsions, or any other condition in which stress due to fever should be avoided. Healthcare providers should be alert to the temperature elevations that may occur following vaccination.

5.3 Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic or other immediate hypersensitivity reactions (*e.g.*, hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. Carefully evaluate the potential risk-to-benefit ratio before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution; adequate treatment should be readily available should a reaction occur *[see Contraindications (4.1)]* {2}.

Children with egg allergy are at low risk for anaphylactic reactions to measles-containing vaccines (including M-M-R II), and skin testing of children allergic to eggs is not predictive of reactions to M-M-R II vaccine. Persons with allergies to chickens or feathers are not at increased risk of reaction to the vaccine {2}.

5.4 Contact Hypersensitivity to Neomycin

Most often, neomycin allergy manifests as a contact dermatitis, which is not a contraindication to receiving measles-, mumps-, rubella-, or varicella-containing vaccine.

5.5 Thrombocytopenia

Carefully evaluate the potential risk-to-benefit ratio before considering vaccination with ProQuad in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of measles, mumps, rubella, and/or varicella vaccine. No clinical data are available regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. Cases of thrombocytopenia have been reported after primary vaccination with measles vaccine; measles, mumps, and rubella vaccine; after varicella vaccination; and following re-vaccination with measles vaccine or M-M-R II *[see Adverse Reactions (6.2)]*.

5.6 Use for Post-Exposure Prophylaxis

The safety and efficacy of ProQuad for use after exposure to measles, mumps, rubella, or varicella have not been established.

5.7 Use in HIV-Infected Children

The safety and efficacy of ProQuad for use in children known to be infected with human immunodeficiency viruses have not been established.

5.8 Risk of Vaccine Virus Transmission

Post-licensing experience with VARIVAX suggests that transmission of varicella vaccine virus may occur between healthy vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella.

High-risk individuals susceptible to varicella include:

- Immunocompromised individuals;
- Pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection;
- Newborn infants of mothers without documented positive history of varicella or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

Vaccine recipients should attempt to avoid, to the extent possible, close association with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.

Excretion of small amounts of the live, attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk. However, transmission of the rubella vaccine virus to infants via breast milk has been documented *[see Use in Specific Populations (8.3)]*.

There are no reports of transmission of the more attenuated Enders' Edmonston strain of measles virus or the Jeryl Lynn™ strain of mumps virus from vaccine recipients to susceptible contacts.

5.9 Immune Globulins and Transfusions

Immune globulins (IG) administered concomitantly with ProQuad contain antibodies that may interfere with vaccine virus replication and decrease the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG.

The appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (*e.g.*, 5 months for Varicella Zoster Immune Globulin [VZIG]) {2}. Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination {2}. *[See Drug Interactions (7.1).]*

5.10 Risk of Transmission of Creutzfeldt-Jakob Disease and Other Adventitious Agents

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. Although there is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), no cases of transmission of CJD or viral disease have ever been identified that were associated with the use of albumin. The cells, virus pools, bovine serum, and human albumin used in manufacturing are all

evaluated and tested to provide assurance that the final product is free of potential adventitious agents *[see Description (11)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

Children 12 Through 23 Months of Age Who Received a Single Dose of ProQuad

ProQuad was administered to 4497 children 12 through 23 months of age involved in 4 randomized clinical trials without concomitant administration with other vaccines. The safety of ProQuad was compared with the safety of M-M-R II and VARIVAX given concomitantly (N=2038) at separate injection sites. The safety profile for ProQuad was similar to the component vaccines. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for 98% of children in each group. Few subjects (<0.1%) who received ProQuad discontinued the study due to an adverse reaction. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 65.2% White; 13.1% African-American; 11.1% Hispanic; 5.8% Asian/Pacific; 4.5% other; and 0.2% American Indian. The racial distribution of the control group was similar to that of the group who received ProQuad. The gender distribution across the studies following a first dose of ProQuad was 52.5% male and 47.5% female. The gender distribution of the control group was similar to that of the group who received ProQuad. Vaccine-related injection-site and systemic adverse reactions observed among recipients of ProQuad or M-M-R II and VARIVAX at a rate of at least 1% are shown in Table 1. Systemic vaccine-related adverse reactions that were reported at a significantly greater rate in individuals who received a first dose of ProQuad than in individuals who received first doses of M-M-R II and VARIVAX concomitantly at separate injection sites were fever (≥102°F [≥38.9°C] oral equivalent or abnormal) (21.5% versus 14.9%, respectively, risk difference 6.6%, 95% CI: 4.6, 8.5), and measles-like rash (3.0% versus 2.1%, respectively, risk difference 1.0%, 95% CI: 0.1, 1.8). Both fever and measles-like rash usually occurred within 5 to 12 days following the vaccination, were of short duration, and resolved with no long-term sequelae. Pain/tenderness/soreness at the injection site was reported at a statistically lower rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites (22.0% versus 26.8%, respectively, risk difference -4.8%, 95% CI: -7.1, -2.5). The only vaccine-related injection-site adverse reaction that was more frequent among recipients of ProQuad than recipients of M-M-R II and VARIVAX was rash at the injection site (2.4% versus 1.6%, respectively, risk difference 0.9%, 95% CI: 0.1, 1.5).

Table 1: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad Dose 1 or M-M-R II and VARIVAX at 12 to 23 Months of Age (0 to 42 Days Postvaccination)

Adverse Reactions	ProQuad (N=4497) (n=4424) %	M-M-R II and VARIVAX (N=2038) (n=1997) %
Injection Site[*]		
Pain/tenderness/soreness[†]	22.0	26.7
Erythema[†]	14.4	15.8
Swelling[†]	8.4	9.8
Ecchymosis	1.5	2.3
Rash	2.3	1.5
Systemic		
Fever[†,‡]	21.5	14.9
Irritability	6.7	6.7
Measles-like rash[†]	3.0	2.1
Varicella-like rash[†]	2.1	2.2
Rash (not otherwise specified)	1.6	1.4
Upper respiratory infection	1.3	1.1

Viral exanthema	1.2	1.1
Diarrhea	1.2	1.3

* Injection-site adverse reactions for M-M-R II and VARIVAX are based on occurrence with either of the vaccines administered.
† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 0 to 4 postvaccination.
‡ Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Rubella-like rashes were observed in <1% of subjects following a first dose of ProQuad.

In these clinical trials, two cases of herpes zoster were reported among 2108 healthy subjects 12 through 23 months of age who were vaccinated with their first dose of ProQuad and followed for 1 year. Both cases were unremarkable and no sequelae were reported.

Children 15 to 31 Months of Age Who Received a Second Dose of ProQuad

In 5 clinical trials, 2780 healthy children were vaccinated with ProQuad (dose 1) at 12 to 23 months of age and then administered a second dose approximately 3 to 9 months later. The race distribution of the study subjects across these studies following a second dose of ProQuad was as follows: 64.4% White; 14.1% African-American; 12.0% Hispanic; 5.9% other; 3.5% Asian/Pacific; and 0.1% American Indian. The gender distribution across the studies following a second dose of ProQuad was 51.5% male and 48.5% female. Children in these open-label studies were monitored for at least 28 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for approximately 97% of children overall. Vaccine-related injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 2. In these trials, the overall rates of systemic adverse reactions after ProQuad (dose 2) were comparable to, or lower than, those seen with the first dose. In the subset of children who received both ProQuad dose 1 and dose 2 in these trials (N=2408) with follow-up for fever, fever ≥102.2°F (≥38.9°C) was observed significantly less frequently days 1 to 28 after the second dose (10.8%) than after the first dose (19.1%) (risk difference 8.3%, 95% CI: 6.4, 10.3). Fevers ≥102.2°F (≥38.9°C) days 5 to 12 after vaccinations were also reported significantly less frequently after dose 2 (3.9%) than after dose 1 (13.6%) (risk difference 9.7%, 95% CI: 8.1, 11.3). In the subset of children who received both doses and for whom injection-site reactions were reported (N=2679), injection-site erythema was noted significantly more frequently after ProQuad (dose 2) as compared to ProQuad (dose 1) (12.6% and 10.8%, respectively, risk difference -1.8, 95% CI: -3.3, -0.3); however, pain and tenderness at the injection site was significantly lower after dose 2 (16.1%) as compared with after dose 1 (21.9%) (risk difference, 5.8%, 95% CI: 4.1, 7.6). Two children had febrile seizures after ProQuad (dose 2); both febrile seizures were thought to be related to a concurrent viral illness *[see Adverse Reactions (6.3) and Clinical Studies (14)]*. These studies were not designed or statistically powered to detect a difference in rates of febrile seizure between recipients of ProQuad as compared to M-M-R II and VARIVAX. The risk of febrile seizure has not been evaluated in a clinical study comparing the incidence rate after ProQuad (dose 2) with the incidence rate after concomitant M-M-R II (dose 2) and VARIVAX (dose 2). *[See Adverse Reactions (6.1), Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX.]*

Table 2: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad Dose 1 at 12 to 23 Months of Age and Dose 2 at 15 to 31 Months of Age (1 to 28 Days Postvaccination)

Adverse Reactions	ProQuad Dose 1 (N=3112) (n=3019) %	ProQuad Dose 2 (N=2780) (n=2695) %
Injection-Site		
Pain/tenderness/soreness*	21.4	15.9
Erythema*	10.7	12.4
Swelling*	8.0	8.5
Injection-site bruising	1.1	0.0
Systemic		
Fever*,†	20.4	8.3
Irritability	6.0	2.4
Measles-like/Rubella-like rash	4.3	0.9

Varicella-like/Vesicular rash	1.5	0.1
Diarrhea	1.3	0.6
Upper respiratory infection	1.3	1.4
Rash (not otherwise specified)	1.2	0.6
Rhinorrhea	1.1	1.0

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
† Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX

In a double-blind clinical trial, 799 healthy 4- to 6-year-old children who received M-M-R II and VARIVAX at least 1 month prior to study entry were randomized to receive ProQuad and placebo (N=399), M-M-R II and placebo concomitantly (N=205) at separate injection sites, or M-M-R II and VARIVAX (N=195) concomitantly at separate injection sites *[see Clinical Studies (14)]*. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for >98% of children in each group. The race distribution of the study subjects following a dose of ProQuad was as follows: 78.4% White; 12.3% African-American; 3.8% Hispanic; 3.5% other; and 2.0% Asian/Pacific. The gender distribution following a dose of ProQuad was 52.1% male and 47.9% female. Injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 3. *[See Clinical Studies (14).]*

Table 3: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Previously Vaccinated with M-M-R II and VARIVAX Who Received ProQuad + Placebo, M-M-R II + Placebo, or M-M-R II + VARIVAX at 4 to 6 Years of Age (1 to 43 Days Postvaccination)

Adverse Reactions	ProQuad + Placebo (N=399) (n=397) %		M-M-R II + Placebo (N=205) (n=205) %		M-M-R II + VARIVAX (N=195) (n=193) %	
Systemic						
Fever*,†	2.5		2.0		4.1	
Cough	1.3		0.5		0.5	
Irritability	1.0		0.5		1.0	
Headache	0.8		1.5		1.6	
Rhinorrhea	0.5		1.0		0.5	
Nasopharyngitis	0.3		1.0		1.0	
Vomiting	0.3		1.0		0.5	
Upper respiratory infection	0.0		0.0		1.0	
	ProQuad %	Placebo %	M-M-R II %	Placebo %	M-M-R II %	VARIVAX %
Injection-Site						
Pain*	41.1	34.5	36.6	34.1	35.2	36.8
Erythema*	24.4	13.4	15.6	14.1	14.5	15.5
Swelling*	15.6	8.1	10.2	8.8	7.8	10.9
Bruising	3.5	3.8	2.4	3.4	1.6	2.1
Rash	1.5	1.3	0.0	0.0	0.5	0.0
Pruritus	1.0	0.3	0.0	0.0	0.0	1.0
Nodule	0.0	0.0	0.0	0.0	0.0	1.0

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
† Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Safety In Trials That Evaluated Concomitant Use with Other Vaccines

ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine

In an open-label clinical trial, 1434 children were randomized to receive ProQuad given with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly (N=949) or non-concomitantly with ProQuad given first and the other vaccines 6 weeks later (N=485). No clinically significant differences in adverse events were reported between treatment groups *[see Clinical Studies (14)]*. The race distribution of the study subjects who received ProQuad was as follows: 70.7% White; 10.9% Asian/Pacific; 10.7% African-American; 4.5% Hispanic; 3.0% other; and 0.2% American Indian. The gender distribution of the study subjects who received ProQuad was 53.6% male and 46.4% female.

ProQuad Administered with Pneumococcal 7-valent Conjugate Vaccine and/or Hepatitis A Vaccine, Inactivated

In an open-label clinical trial, 1027 healthy children 12 to 23 months of age were randomized to receive ProQuad (dose 1) and pneumococcal 7-valent conjugate vaccine (dose 4) concomitantly (N=510) or non-concomitantly at different clinic visits (N=517). The race distribution of the study subjects was as follows: 65.2% White; 15.1% African-American; 10.0% Hispanic; 6.6% other; and 3.0% Asian/Pacific. The gender distribution of the study subjects was 54.5% male and 45.5% female. Injection-site and systemic adverse reactions observed among recipients of ProQuad administered concomitantly or non-concomitantly with pneumococcal 7-valent conjugate vaccine at a rate of at least 1% are shown in Table 4. No clinically significant differences in adverse reactions were reported between the concomitant and non-concomitant treatment groups *[see Clinical Studies (14)]*.

Table 4: Vaccine-Related Injection-Site and Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad (dose 1) Concomitantly or Non-Concomitantly with PCV7* (dose 4) at the First Visit (1 to 28 Days Postvaccination)

Adverse Reactions	ProQuad + PCV7 (N=510) (n=498) %	PCV7 (N=258) (n=250) %	ProQuad (N=258) (n=255) %
Injection-Site - ProQuad			
Pain†	24.9	N/A	24.7
Erythema†	12.4	N/A	11.0
Swelling†	10.8	N/A	7.5
Bruising	2.0	N/A	1.6
Injection-Site - PCV7			
Pain†	30.5	29.6	N/A
Erythema†	21.1	24.4	N/A
Swelling†	17.9	20.0	N/A
Bruising	1.6	1.2	N/A
Systemic			
Fever†,‡	15.5	10.0	15.3
Measles-like rash	4.4	0.8	5.1
Irritability	3.8	3.6	3.5
Upper respiratory infection	1.6	0.8	1.2
Varicella-like/vesicular rash	1.6	0.0	1.2
Diarrhea	0.8	1.2	1.2
Vomiting	0.6	0.8	1.2
Rash	0.4	0.0	1.2
Somnolence	0.0	0.0	1.2

* PCV7 = Pneumococcal 7-valent conjugate vaccine, dose 4.
† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
‡ Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
N/A = Not applicable.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

In an open-label clinical trial, 699 healthy children 12 to 23 months of age were randomized to receive 2 doses of VAQTA® (hepatitis A vaccine, inactivated) (N=352) or 2 doses of VAQTA concomitantly with 2 doses of ProQuad (N=347) at least 6 months apart. An additional 1101 subjects received 2 doses of VAQTA alone at least 6 months apart (non-randomized), resulting in 1453 subjects receiving 2 doses of VAQTA alone (1101 non-randomized and 352 randomized) and 347 subjects receiving 2 doses of VAQTA concomitantly with ProQuad (all randomized). The race distribution of the study subjects following

a dose of ProQuad was as follows: 47.3% White; 42.7% Hispanic; 5.5% other; 2.9% African-American; and 1.7% Asian/Pacific. The gender distribution of the study subjects following a dose of ProQuad was 49.3% male and 50.7% female. Vaccine-related injection-site adverse reactions (days 1 to 5 postvaccination) and systemic adverse events (days 1 to 14 post VAQTA and days 1 to 28 post ProQuad vaccination) observed among recipients of VAQTA and ProQuad administered concomitantly with VAQTA at a rate of at least 1% are shown in Tables 5 and 6, respectively. In addition, among the randomized cohort, in the 14 days after each vaccination, the rates of fever (including all vaccine- and non-vaccine-related reports) were significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 1 (22.0%) as compared to subjects given dose 1 of VAQTA without ProQuad (10.8%). However, rates of fever were not significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 2 (12.5%) as compared to subjects given dose 2 of VAQTA without ProQuad (9.4%). In post-hoc analyses, these rates were significantly different for dose 1 (relative risk (RR) 2.03 [95% CI: 1.42, 2.94]), but not dose 2 (RR 1.32 [95% CI: 0.82, 2.13]). Rates of injection-site adverse reactions and other systemic adverse events were lower following a second dose than following the first dose of both vaccines given concomitantly.

Table 5: Vaccine-Related Injection-Site Adverse Reactions Reported in ≥1% of Children Who Received VAQTA or ProQuad Concomitantly with VAQTA 1 to 5 Days After Vaccination with VAQTA or VAQTA and ProQuad

Adverse Reactions	Dose 1		Dose 2	
	VAQTA (N=1453) (n=1412) %	ProQuad + VAQTA (N=347) (n=328) %	VAQTA (N=1301) (n=1254) %	ProQuad + VAQTA (N=292) (n=264) %
Injection-Site - VAQTA				
Pain/tenderness*	29.2	27.1	30.1	25.0
Erythema*	13.5	12.5	14.3	11.7
Swelling*	7.1	9.1	9.0	8.0
Injection-site bruising	1.9	2.4	1.0	0.8
Injection-Site - ProQuad				
Pain/tenderness*	N/A	30.5	N/A	26.2
Erythema*	N/A	13.4	N/A	12.9
Swelling*	N/A	6.7	N/A	6.5
Injection-site bruising	N/A	1.5	N/A	0.4

* Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.
N/A = Not applicable.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Table 6: Vaccine-Related Systemic Adverse Reactions Reported in ≥1% of Children Who Received VAQTA* or ProQuad Concomitantly with VAQTA 1 to 14 Days After VAQTA or Vaccination with ProQuad and VAQTA and 1 to 28 Days After Vaccination with ProQuad and VAQTA

Adverse Reactions	Dose 1			Dose 2		
	Days 1 to 14		Days 1 to 28	Days 1 to 14		Days 1 to 28
	VAQTA† (N=1453) (n=1412) %	ProQuad + VAQTA† (N=347) (n=328) %	ProQuad + VAQTA (N=347) (n=328) %	VAQTA (N=1301) (n=1254) %	ProQuad + VAQTA† (N=292) (n=264) %	ProQuad + VAQTA† (N=291) (n=263) %
Fever‡§	5.7	14.9	15.2	4.1	8.0	8.4
Irritability	5.8	7.0	7.3	3.5	5.3	5.3
Measles-like rash	0.0	3.4	3.4	0.0	1.1	1.1
Rhinorrhea	0.6	2.7	3.0	0.6	1.1	2.7
Diarrhea	1.5	1.8	2.4	1.7	0.4	0.8
Cough	0.6	2.1	2.1	0.2	0.8	1.5
Vomiting	1.1	0.3	0.9	0.6	0.8	1.1

* Systemic adverse events for subjects given VAQTA alone were collected for 14 days postvaccination.
† Safety follow-up for systemic adverse reactions was 14 days for VAQTA and 28 days for ProQuad + VAQTA.

‡ Designates a solicited adverse reaction.
§ Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

In an open-label clinical trial, 653 children 12 to 23 months of age were randomized to receive a first dose of ProQuad with VAQTA and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or a first dose of ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly and then vaccinated with VAQTA 6 weeks later (N=323). Approximately 6 months later, subjects received either the second doses of ProQuad and VAQTA concomitantly or the second doses of ProQuad and VAQTA separately. The race distribution of the study subjects was as follows: 60.3% White; 21.6% African-American; 9.5% Hispanic; 7.2% other; 1.1% Asian/Pacific; and 0.3% American Indian. The gender distribution of the study subjects was 50.7% male and 49.3% female. Vaccine-related injection-site and systemic adverse reactions observed among recipients of concomitant ProQuad, VAQTA, and pneumococcal 7-valent conjugate vaccine and ProQuad and pneumococcal 7-valent conjugate vaccine at a rate of at least 1% are shown in Tables 7 and 8. In the 28 days after vaccination with the first dose of ProQuad, the rates of fever (including all vaccine- and non-vaccine-related reports) were comparable in subjects who received the 3 vaccines together (38.6%) as compared with subjects given ProQuad and pneumococcal 7-valent conjugate vaccine (42.7%). The rates of fever in the 28 days following the second dose of ProQuad were also comparable in subjects who received ProQuad and VAQTA together (17.4%) as compared with subjects given ProQuad separately from VAQTA (17.0%). In a post-hoc analysis, these differences were not statistically significant after ProQuad (dose 1) (RR 0.90 [95% CI: 0.75, 1.09]) nor after dose 2 (RR 1.02 [95% CI: 0.70, 1.51]). No clinically significant differences in adverse reactions were reported among treatment groups *[see Clinical Studies (14)]*.

Table 7: Vaccine-Related Injection-Site Adverse Reactions Reported in ≥1% of Children Who Received ProQuad + VAQTA + PCV7* Concomitantly or VAQTA Alone Followed by ProQuad + PCV7 Concomitantly (1 to 5 Days After a Dose of ProQuad)

Adverse Reactions	Dose 1		Dose 2	
	VAQTA + ProQuad + PCV7 (N=330) (n=311) %	VAQTA Alone Followed by ProQuad + PCV7 (N=323) (n=302) %	VAQTA + ProQuad (N=273) (n=265) %	VAQTA Alone Followed by ProQuad (N=240) (n=230) %
Injection-Site - ProQuad				
Pain/tenderness†	21.2	24.2	18.1	17.0
Erythema†	13.5	11.9	10.6	13.0
Swelling†	7.4	10.9	8.3	11.7
Bruising	1.9	1.3	0.8	0.4
Injection-Site - VAQTA				
Pain/tenderness†	20.6	15.3	17.5	20.3
Erythema†	9.6	11.7	9.1	12.7
Swelling†	6.8	9.5	6.1	7.6
Bruising	1.3	1.1	1.1	1.6
Rash	1.0	0.0	0.4	0.4
Injection-Site - PCV7				
Pain/tenderness†	25.4	27.6	N/A	N/A
Erythema†	16.4	16.6	N/A	N/A
Swelling†	13.2	14.3	N/A	N/A
Bruising	0.6	1.7	N/A	N/A

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
† Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination at each vaccine injection site.
N/A = Not applicable.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Table 8: Vaccine-Related Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad + VAQTA + PCV7* Concomitantly, or VAQTA Alone Followed by ProQuad + PCV7 Concomitantly (1 to 28 Days After a Dose of ProQuad)

Adverse Reactions	Dose 1		Dose 2	
	VAQTA + ProQuad + PCV7 (N=330) (n=311) %	VAQTA Alone Followed by ProQuad + PCV7 (N=323) (n=302) %	VAQTA + ProQuad (N=273) (n=265) %	VAQTA Alone Followed by ProQuad (N=240) (n=230) %
Fever†‡	26.4	27.2	9.1	9.6
Irritability	4.8	6.3	1.9	1.3
Measles-like rash†	2.3	4.0	0.0	0.0
Varicella-like rash†	1.0	1.7	0.0	0.0
Rash (not otherwise specified)	1.3	1.3	0.0	0.9
Diarrhea	1.3	1.3	0.4	1.3
Upper respiratory infection	1.0	1.3	1.1	0.9
Viral infection	1.0	0.7	0.0	0.0
Rhinorrhea	0.0	0.7	1.1	0.0

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
† Designates a solicited adverse reaction.
‡ Temperature reported as elevated or abnormal.
N = number of subjects vaccinated.
n = number of subjects with safety follow-up.

Reye syndrome following wild-type varicella infection has occurred in children and adolescents, the majority of whom had received salicylates. In all clinical studies of ProQuad or VARIVAX, the recommendation was made to avoid the use of salicylates for 6 weeks after vaccination. There were no reports of Reye syndrome in recipients of ProQuad or VARIVAX during these studies *[see Drug Interactions (7.2) and Patient Counseling Information (17)]*.

6.2 Post-Marketing Experience

The following adverse events have been identified during post-approval use of either the components of ProQuad or ProQuad. Because the events are in some cases described in the literature or reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Post-Marketing Reports

Adverse events reported with post-marketing use of ProQuad and/or in clinical studies and/or post-marketing use of M-M-R II, the component vaccines, and VARIVAX without regard to causality or frequency are summarized below.

Infections and infestations

Atypical measles, candidiasis, cellulitis, herpes zoster, infection, influenza, measles, orchitis, parotitis, respiratory infection, skin infection, varicella (vaccine strain).

Blood and the lymphatic system disorders

Aplastic anemia, lymphadenitis, regional lymphadenopathy, thrombocytopenia.

Immune system disorders

Anaphylactoid reaction, anaphylaxis and related phenomena such as angioneurotic edema, facial edema, and peripheral edema, anaphylaxis in individuals with or without an allergic history.

Psychiatric disorders

Agitation, apathy, nervousness.

Nervous system disorders

Acute disseminated encephalomyelitis (ADEM), afebrile convulsions or seizures, aseptic meningitis (see below), ataxia, Bell's palsy, cerebrovascular accident, convulsion, dizziness, dream abnormality, encephalitis (see below), encephalopathy (see below), febrile seizure, Guillain-Barré syndrome, headache, hypersomnia, measles inclusion body encephalitis *[see Contraindications (4.2)]*, ocular palsies, paraesthesia, polyneuritis, polyneuropathy, subacute sclerosing panencephalitis (see below), syncope, transverse myelitis, tremor.

Eye disorders

Edema of the eyelid, irritation, necrotizing retinitis (in immunocompromised individuals), optic neuritis, retinitis, retrobulbar neuritis.

Ear and labyrinth disorders

Ear pain, nerve deafness.

Vascular disorders

Extravasation.

Respiratory, thoracic and mediastinal disorders

Bronchial spasm, bronchitis, epistaxis, pneumonitis *[see Contraindications (4.3)]*, pneumonia, pulmonary congestion, rhinitis, sinusitis, sneezing, sore throat, wheezing.

Gastrointestinal disorders

Abdominal pain, flatulence, hematochezia, mouth ulcer.

Skin and subcutaneous tissue disorders

Erythema multiforme, Henoch-Schönlein purpura, herpes simplex, impetigo, panniculitis, pruritus, purpura, skin induration, Stevens-Johnson syndrome, sunburn.

Musculoskeletal, connective tissue and bone disorders

Arthritis and/or arthralgia (usually transient and rarely chronic, see below); musculoskeletal pain; myalgia; pain of the hip, leg, or neck; swelling.

Reproductive system and breast disorders

Epididymitis.

General disorders and administration site conditions

Injection-site complaints (burning and/or stinging of short duration, eczema, edema/swelling, hive-like rash, discoloration, hematoma, induration, lump, vesicles, wheal and flare), inflammation, lip abnormality, papillitis, roughness/dryness, stiffness, trauma, varicella-like rash, venipuncture site hemorrhage, warm sensation, warm to touch.

Deaths have been reported following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals. Death as a direct consequence of disseminated measles vaccine virus infection has been reported in severely immunocompromised individuals in whom a measles-containing vaccine is contraindicated and who were inadvertently vaccinated. However, there were no deaths or permanent sequelae reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993 {3}.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines. The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases) {4,5}.

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported *[see Contraindications (4.2)]*. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

Recipients of rubella vaccine may develop chronic joint symptoms. Arthralgia and/or arthritis, and polyneuritis after wild-type rubella virus infection vary in frequency and severity with age and gender, being greatest in adult females and least in pre-pubertal children. Following vaccination in children, reactions in joints are uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are higher than those seen in children (12 to 26%), and the reactions tend to be more marked and of longer duration (*e.g.*, months or years). In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Chronic joint symptoms have been reported following administration of rubella-containing vaccine.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated measles vaccine distribution in the United States (US), the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. The association with wild-type measles virus infection is 6 to 22 cases of SSPE per million cases of measles. The results

of a retrospective case-controlled study suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

Cases of aseptic meningitis have been reported to Vaccine Adverse Event Reporting System (VAERS) following measles, mumps, and rubella vaccination. Although a causal relationship between other strains of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Cases of thrombocytopenia have been reported after use of measles vaccine; measles, mumps, and rubella vaccine; and after varicella vaccination. Post-marketing experience with live measles, mumps, and rubella vaccine indicates that individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia following the first dose of a live measles, mumps, and rubella vaccine may develop thrombocytopenia with repeat doses. Serologic testing for antibody to measles, mumps, or rubella should be considered in order to determine if additional doses of vaccine are needed *[see Warnings and Precautions (5.5)]*.

The reported rate of zoster in recipients of VARIVAX appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella {6}. In clinical trials, 8 cases of herpes zoster were reported in 9454 vaccinated individuals 12 months to 12 years of age during 42,556 person-years of follow-up. This resulted in a calculated incidence of at least 18.8 cases per 100,000 person-years. All 8 cases reported after VARIVAX were mild and no sequelae were reported. The long-term effect of VARIVAX on the incidence of herpes zoster is unknown at present.

6.3 Post-Marketing Observational Safety Surveillance Study

Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old. A historical comparison group included 69,237 age-, gender-, and date-of-vaccination (day and month) matched subjects who were given M-M-R II and VARIVAX concomitantly. The primary objective was to assess the incidence of febrile seizures occurring within various time intervals after vaccination in 12- to 60-month-old children who had neither been vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections (N=31,298 vaccinated with ProQuad, including 31,043 who were 12 to 23 months old). The incidence of febrile seizures was also assessed in a historical control group of children who had received their first vaccination with M-M-R II and VARIVAX concomitantly (N=31,298, including 31,019 who were 12 to 23 months old). The secondary objective was to assess the general safety of ProQuad in the 30-day period after vaccination in children 12 months to 12 years old.

In pre-licensure clinical studies, an increase in fever was observed 5 to 12 days after vaccination with ProQuad (dose 1) compared to M-M-R II and VARIVAX (dose 1) given concomitantly. In the post-marketing observational surveillance study, results from the primary safety analysis revealed an approximate two-fold increase in the risk of febrile seizures in the same 5 to 12 day timeframe after vaccination with ProQuad (dose 1). The incidence of febrile seizures 5 to 12 days after ProQuad (dose 1) (0.70 per 1000 children) was higher than that in children receiving M-M-R II and VARIVAX concomitantly (0.32 per 1000 children) [RR 2.20, 95% confidence interval (CI): 1.04, 4.65]. The incidence of febrile seizures 0 to 30 days after ProQuad (dose 1) (1.41 per 1000 children) was similar to that observed in children receiving M-M-R II and VARIVAX concomitantly [RR 1.10 (95% CI: 0.72, 1.69)]. See Table 9. General safety analyses revealed that the risks of fever (RR=1.89; 95% CI: 1.67, 2.15) and skin eruption (RR=1.68; 95% CI: 1.07, 2.64) were significantly higher after ProQuad (dose 1) compared with those who received concomitant first doses of M-M-R II and VARIVAX, respectively. All medical events that resulted in hospitalization or emergency room visits were compared between the group given ProQuad and the historical comparison group, and no other safety concerns were identified in this study.

Table 9: Confirmed Febrile Seizures Days 5 to 12 and 0 to 30 After Vaccination with ProQuad (dose 1) Compared to Concomitant Vaccination with M-M-R II and VARIVAX (dose 1) in Children 12 to 60 Months of Age

Time Period	ProQuad cohort (N=31,298)		MMR+V cohort (N=31,298)		Relative risk (95% CI)
	n	Incidence per 1000	n	Incidence per 1000	
5 to 12 Days	22	0.70	10	0.32	2.20 (1.04, 4.65)
0 to 30 Days	44	1.41	40	1.28	1.10 (0.72, 1.69)

In this observational post-marketing study, no case of febrile seizure was observed during the 5 to 12 day post-vaccination time period among 26,455 children who received ProQuad as a second dose of

M-M-R II and VARIVAX. In addition, detailed general safety data were available from more than 25,000 children who received ProQuad as a second dose of M-M-R II and VARIVAX, most of them (95%) between 4 and 6 years of age, and an analysis of these data by an independent, external safety monitoring committee did not identify any specific safety concern.

7 DRUG INTERACTIONS

7.1 Immune Globulins and Transfusions

Immune globulins (IG) administered concomitantly with ProQuad contain antibodies that may interfere with vaccine virus replication and decrease the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG.

The appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (*e.g.*, 5 months for Varicella Zoster Immune Globulin [VZIG]) {2}. Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination {2}. *[See Warnings and Precautions (5.9).]*

7.2 Salicylates

Reye syndrome has been reported following the use of salicylates during wild-type varicella infection. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad. *[See Adverse Reactions (6.1) and Patient Counseling Information (17).]*

7.3 Corticosteroids and Immunosuppressive Drugs

ProQuad may be used in individuals who are receiving topical corticosteroids or low-dose corticosteroids for asthma prophylaxis or replacement therapy, *e.g.*, for Addison's disease. ProQuad should not be given to individuals receiving immunosuppressive doses of corticosteroids or other immunosuppressive drugs. Vaccination with a live, attenuated vaccine, such as varicella or measles, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive drugs *[see Contraindications (4.2)]*.

7.4 Drug/Laboratory Test Interactions

Live, attenuated measles, mumps, and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after ProQuad.

7.5 Use with Other Vaccines

At least 1 month should elapse between a dose of a measles-containing vaccine such as M-M-R II and a dose of ProQuad, and at least 3 months should elapse between administration of 2 doses of ProQuad or varicella-containing vaccines.

ProQuad may be administered concomitantly with *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant). Additionally, ProQuad may be administered concomitantly with pneumococcal 7-valent conjugate vaccine, and/or hepatitis A (inactivated) vaccines. *[See Clinical Studies (14).]*

There are no data regarding the administration of ProQuad with inactivated poliovirus vaccine or with other live virus vaccines.

There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed. *[See Clinical Studies (14).]*

Children under treatment for tuberculosis have not experienced exacerbation of the disease when vaccinated with live measles virus vaccine; no studies have been reported to date of the effect of measles virus vaccines on children with untreated tuberculosis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category: Contraindication *[see Contraindications (4.4)]*.

Do not administer ProQuad to pregnant females. It is also not known whether ProQuad can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. *[See Contraindications (4.4) and Patient Counseling Information (17).]*

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the healthcare provider should be aware of the following: (1) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to wild-type measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects; (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans {7}; (3) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome {8}; and (4) Wild-type varicella can sometimes cause congenital varicella infection.

Pregnancy Registry

From 1995 to 2013, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintained a Pregnancy Registry to monitor fetal outcomes following inadvertent administration of VARIVAX during pregnancy or within three months prior to conception. In 2006, reports of exposure to two other varicella (Oka/Merck)-containing vaccines, ProQuad and ZOSTAVAX® (Zoster Vaccine Live), were added to the Registry. The Pregnancy Registry has been discontinued. As of March 2011, 811 women with pregnancy outcome information available for analysis were prospectively enrolled following vaccination with VARIVAX, within three months prior to conception or any time during pregnancy. Of these women, 170 were seronegative at the time of exposure and 627 women had an unknown serostatus. The remaining women were seropositive. Nine exposures to either ProQuad or ZOSTAVAX have been reported that met criteria for inclusion into the Registry.

None of the 820 women who received a varicella-containing vaccine delivered infants with abnormalities consistent with congenital varicella syndrome.

All exposures to VARIVAX, ProQuad, or ZOSTAVAX during pregnancy or within three months prior to conception should be reported as suspected adverse reactions by contacting Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

8.3 Nursing Mothers

Do not administer ProQuad to nursing women. It is not known whether ProQuad is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ProQuad is administered to a nursing woman. The secretion of measles and mumps viruses in human milk has not been studied; however, studies have shown that lactating postpartum women vaccinated with live rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. Limited evidence in the literature suggests that virus, viral DNA, or viral antigen could not be detected in the breast milk of women who were vaccinated postpartum with the vaccine strain of varicella virus {9,10}. *[See Warnings and Precautions (5.8).]*

8.4 Pediatric Use

Do not administer ProQuad to infants younger than 12 months of age or to children 13 years and older. Safety and effectiveness of ProQuad in infants younger than 12 months of age and in children 13 years and older have not been studied. ProQuad is not approved for use in persons in these age groups. *[See Adverse Reactions (6) and Clinical Studies (14).]*

8.5 Geriatric Use

ProQuad is not indicated for use in the geriatric population (≥age 65).

11 DESCRIPTION

ProQuad (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) is a combined, attenuated, live virus vaccine containing measles, mumps, rubella, and varicella viruses. ProQuad is a sterile lyophilized preparation of (1) the components of M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live): Measles Virus Vaccine Live, a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; Rubella Virus Vaccine

Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts; and (2) Varicella Virus Vaccine Live (Oka/Merck), the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells. The cells, virus pools, bovine serum, and human albumin used in manufacturing are all tested to provide assurance that the final product is free of potential adventitious agents.

ProQuad, when reconstituted as directed, is a sterile suspension for subcutaneous administration. Each 0.5-mL dose contains not less than 3.00 $\log_{10}$ $TCID_{50}$ of measles virus; 4.30 $\log_{10}$ $TCID_{50}$ of mumps virus; 3.00 $\log_{10}$ $TCID_{50}$ of rubella virus; and a minimum of 3.99 $\log_{10}$ PFU of Oka/Merck varicella virus.

Each 0.5-mL dose of the vaccine contains no more than 21 mg of sucrose, 11 mg of hydrolyzed gelatin, 2.4 mg of sodium chloride, 1.8 mg of sorbitol, 0.40 mg of monosodium L-glutamate, 0.34 mg of sodium phosphate dibasic, 0.31 mg of human albumin, 0.17 mg of sodium bicarbonate, 72 mcg of potassium phosphate monobasic, 60 mcg of potassium chloride; 36 mcg of potassium phosphate dibasic; residual components of MRC-5 cells including DNA and protein; <16 mcg of neomycin, bovine calf serum (0.5 mcg), and other buffer and media ingredients. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ProQuad has been shown to induce measles-, mumps-, rubella-, and varicella-specific immunity, which is thought to be the mechanism by which it protects against these four childhood diseases.

The efficacy of ProQuad was established through the use of immunological correlates for protection against measles, mumps, rubella, and varicella. Results from efficacy studies or field effectiveness studies that were previously conducted for the component vaccines were used to define levels of serum antibodies that correlated with protection against measles, mumps, and rubella. Also, in previous studies with varicella vaccine, antibody responses against varicella virus ≥5 gpELISA units/mL in a glycoprotein enzyme-linked immunosorbent assay (gpELISA) (not commercially available) similarly correlated with long-term protection. In these efficacy studies, the clinical endpoint for measles and mumps was a clinical diagnosis of either disease confirmed by a 4-fold or greater rise in serum antibody titers between either postvaccination or acute and convalescent titers; for rubella, a 4-fold or greater rise in antibody titers with or without clinical symptoms of rubella; and for varicella, varicella-like rash that occurred >42 days postvaccination and for which varicella was not excluded by either viral cultures of the lesion or serological tests. Specific laboratory evidence of varicella either by serology or culture was not required to confirm the diagnosis of varicella. Clinical studies with a single dose of ProQuad have shown that vaccination elicited rates of antibody responses against measles, mumps, and rubella that were similar to those observed after vaccination with a single dose of M-M-R II *[see Clinical Studies (14)]* and seroresponse rates for varicella virus were similar to those observed after vaccination with a single dose of VARIVAX *[see Clinical Studies (14)]*. The duration of protection from measles, mumps, rubella, and varicella infections after vaccination with ProQuad is unknown.

12.4 Persistence of Antibody Responses after Vaccination

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2107 children enrolled in the clinical trials. Antibody was detected in 98.9% (1722/1741) for measles, 96.7% (1676/1733) for mumps, 99.6% (1796/1804) for rubella, and 97.5% (1512/1550) for varicella (≥5 gpELISA units/mL) of vaccinees following a single dose of ProQuad.

Experience with M-M-R II demonstrates that antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination {11}. Varicella antibodies were present for up to ten years postvaccination in most of the individuals tested who received 1 dose of VARIVAX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ProQuad has not been evaluated for its carcinogenic, mutagenic, or teratogenic potential, or its potential to impair fertility.

14 CLINICAL STUDIES

Formal studies to evaluate the clinical efficacy of ProQuad have not been performed.

Efficacy of the measles, mumps, rubella, and varicella components of ProQuad was previously established in a series of clinical studies with the monovalent vaccines. A high degree of protection from infection was demonstrated in these studies {12-19}.

Immunogenicity in Children 12 Months to 6 Years of Age

Prior to licensure, immunogenicity was studied in 5845 healthy children 12 months to 6 years of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 5 randomized clinical trials. The immunogenicity of ProQuad was similar to that of its individual component vaccines (M-M-R II and VARIVAX), which are currently used in routine vaccination.

The presence of detectable antibody was assessed by an appropriately sensitive enzyme-linked immunosorbent assay (ELISA) for measles, mumps (wild-type and vaccine-type strains), and rubella, and by gpELISA for varicella. For evaluation of vaccine response rates, a positive result in the measles ELISA corresponded to measles antibody concentrations of ≥255 mIU/mL when compared to the WHO II (66/202) Reference Immunoglobulin for Measles.

Children were positive for mumps antibody if the antibody level was ≥10 ELISA units/mL. A positive result in the rubella ELISA corresponded to concentrations of ≥10 IU rubella antibody/mL when compared to the WHO International Reference Serum for Rubella; children with varicella antibody levels ≥5 gpELISA units/mL were considered to be seropositive since a response rate based on ≥5 gpELISA units/mL has been shown to be highly correlated with long-term protection.

Immunogenicity in Children 12 to 23 Months of Age After a Single Dose

In 4 randomized clinical trials, 5446 healthy children 12 to 23 months of age were administered ProQuad, and 2038 children were vaccinated with M-M-R II and VARIVAX given concomitantly at separate injection sites. Subjects enrolled in each of these trials had a negative clinical history, no known recent exposure, and no vaccination history for varicella, measles, mumps, and rubella. Children were excluded from study participation if they had an immune impairment or had a history of allergy to components of the vaccine(s). Except for in 1 trial *[see ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine below]*, no concomitant vaccines were permitted during study participation. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 66.3% White; 12.7% African-American; 9.9% Hispanic; 6.7% Asian/Pacific; 4.2% other; and 0.2% American Indian. The gender distribution of the study subjects across these studies following a first dose of ProQuad was 52.6% male and 47.4% female. A summary of combined immunogenicity results 6 weeks following administration of a single dose of ProQuad or M-M-R II and VARIVAX is shown in Table 10. These results were similar to the immune response rates induced by concomitant administration of single doses of M-M-R II and VARIVAX at separate injection sites (lower bound of the 95% CI for the risk difference in measles, mumps, and rubella seroconversion rates were >-5.0 percentage points and the lower bound of the 95% CI for the risk difference in varicella seroprotection rates was either >-15 percentage points [one study] or >-10.0 percentage points [three studies]).

Table 10: Summary of Combined Immunogenicity Results 6 Weeks Following the Administration of a Single Dose of ProQuad (Varicella Virus Potency ≥3.97 $\log_{10}$ PFU) or M-M-R II and VARIVAX (Per-Protocol Population)

Group	Antigen	n	Observed Response Rate (95% CI)	Observed GMT (95% CI)
ProQuad (N=5446*)	Varicella	4381	91.2% (90.3%, 92.0%)	15.5 (15.0, 15.9)
	Measles	4733	97.4% (96.9%, 97.9%)	3124.9 (3038.9, 3213.3)
	Mumps (OD cutoff)†	973	98.8% (97.9%, 99.4%)	105.3 (98.0, 113.1)
	Mumps (wild-type ELISA)†	3735	95.8% (95.1%, 96.4%)	93.1 (90.2, 96.0)
	Rubella	4773	98.5% (98.1%, 98.8%)	91.8 (89.6, 94.1)
M-M-R II + VARIVAX (N=2038*)	Varicella	1417	94.1% (92.6%, 95.3%)	16.6 (15.9, 17.4)

	Measles	1516	98.2% (97.4%, 98.8%)	2239.6 (2138.3, 2345.6)
	Mumps (OD cutoff)†	501	99.4% (98.3%, 99.9%)	87.5 (79.7, 96.0)
	Mumps (wild-type ELISA)†	1017	98.0% (97.0%, 98.8%)	90.8 (86.2, 95.7)
	Rubella	1528	98.5% (97.7%, 99.0%)	102.2 (97.8, 106.7)

* Includes ProQuad + Placebo followed by ProQuad (Visit 1) (Protocol 009), ProQuad Middle and High Doses (Visit 1) (Protocol 011), ProQuad (Lot 1, Lot 2, Lot 3) (Protocol 012), both the Concomitant and Non-concomitant groups (Protocol 013).

† The mumps antibody response was assessed by a vaccine-strain ELISA in Protocols 009 and 011 and by a wild-type ELISA in Protocols 012 and 013. In the former assay, the serostatus was based on the OD cutoff of the assay. In the latter assay, 10 mumps ELISA units was used as the serostatus cutoff.

n = Number of per-protocol subjects with evaluable serology.
CI = Confidence interval.
GMT = Geometric mean titer.
ELISA = Enzyme-linked immunosorbent assay.
PFU = Plaque-forming units.
OD = Optical density.

Immunogenicity in Children 15 to 31 Months of Age After a Second Dose of ProQuad

In 2 of the 4 randomized clinical trials described above, a subgroup (N=1035) of the 5446 children administered a single dose of ProQuad were administered a second dose of ProQuad approximately 3 to 9 months after the first dose. Children were excluded from receiving a second dose of ProQuad if they were recently exposed to or developed varicella, measles, mumps, and/or rubella prior to receipt of the second dose. No concomitant vaccines were administered to these children. The race distribution across these studies following a second dose of ProQuad was as follows: 67.3% White; 14.3% African-American; 8.3% Hispanic; 5.4% Asian/Pacific; 4.4% other; 0.2% American Indian; and 0.10% mixed. The gender distribution of the study subjects across these studies following a second dose of ProQuad was 50.4% male and 49.6% female. A summary of immune responses following a second dose of ProQuad is presented in Table 11. Results from this study showed that 2 doses of ProQuad administered at least 3 months apart elicited a positive antibody response to all four antigens in greater than 98% of subjects. The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2-fold each for measles, mumps, and rubella, and approximately 41-fold for varicella.

Table 11: Summary of Immune Response to a First and Second Dose of ProQuad in Subjects <3 Years of Age Who Received ProQuad with a Varicella Virus Dose ≥3.97 Log_{10} PFU*

		Dose 1 N=1097			Dose 2 N=1097		
Antigen	Serostatus Cutoff/ Response Criteria	n	Observed Response Rate (95% CI)	Observed GMT (95% CI)	n	Observed Response Rate (95% CI)	Observed GMT (95% CI)
Measles	≥120 mIU/mL†	915	98.1% (97.0%, 98.9%)	2956.8 (2786.3, 3137.7)	915	99.5% (98.7%, 99.8%)	5958.0 (5518.9, 6432.1)
	≥255 mIU/mL	943	97.8% (96.6%, 98.6%)	2966.0 (2793.4, 3149.2)	943	99.4% (98.6%, 99.8%)	5919.3 (5486.2, 6386.6)
Mumps	≥OD Cutoff (ELISA antibody units)	920	98.7% (97.7%, 99.3%)	106.7 (99.1, 114.8)	920	99.9% (99.4%, 100%)	253.1 (237.9, 269.2)
Rubella	≥10 IU/mL	937	97.7% (96.5%, 98.5%)	91.1 (85.9, 96.6)	937	98.3% (97.2%, 99.0%)	158.8 (149.1, 169.2)
Varicella	<1.25 to ≥5 gpELISA	864	86.6% (84.1%,	11.6 (10.9, 12.3)	864	99.4% (98.7%, 99.8%)	477.5 (437.8, 520.7)

	units ≥OD Cutoff (gpELISA units)	695	88.8%) 87.2% (84.5%, 89.6%)	11.6 (10.9, 12.4)	695	99.4% (98.5%, 99.8%)	478.7 (434.8, 527.1)

* Includes the following treatment groups: ProQuad + Placebo followed by ProQuad (Visit 1) (Protocol 009) and ProQuad (Middle and High Dose) (Protocol 011).
† Samples from Protocols 009 and 011 were assayed in the legacy format Measles ELISA, which reported antibody titers in Measles ELISA units. To convert titers from ELISA units to mIU/mL, titers for these 2 protocols were divided by 0.1025. The lowest measurable titer postvaccination is 207.5 mIU/mL. The response rate for measles in the legacy format is the percent of subjects with a negative baseline measles antibody titer, as defined by the optical density (OD) cutoff, with a postvaccination measles antibody titer ≥207.5 mIU/mL.
Samples from Protocols 009 and 011 were assayed in the legacy format Rubella ELISA, which reported antibody titers in Rubella ELISA units. To convert titers from ELISA units to IU/mL, titers for these 2 protocols were divided by 1.28.
ProQuad (Middle Dose) = ProQuad containing a varicella virus dose of 3.97 $\log_{10}$ PFU.
ProQuad (High Dose) = ProQuad containing a varicella virus dose of 4.25 $\log_{10}$ PFU.
ELISA = Enzyme-linked immunosorbent assay.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
N = Number vaccinated at baseline.
n = Number of subjects who were per-protocol Postdose 1 and Postdose 2 and satisfied the given prevaccination serostatus cutoff.
CI = Confidence interval.
GMT = Geometric mean titer.
PFU = Plaque-forming units.

Immunogenicity in Children 4 to 6 Years of Age Who Received a First Dose of ProQuad After Primary Vaccination With M-M-R II and VARIVAX

In a clinical trial, 799 healthy 4- to 6-year-old children who had received M-M-R II and VARIVAX at least 1 month prior to study entry were randomized to receive ProQuad and placebo (N=399), M-M-R II and placebo concomitantly at separate injection sites (N=205), or M-M-R II and VARIVAX concomitantly at separate injection sites (N=195). Children were eligible if they were previously administered primary doses of M-M-R II and VARIVAX, either concomitantly or non-concomitantly, at 12 months of age or older. Children were excluded if they were recently exposed to measles, mumps, rubella, and/or varicella, had an immune impairment, or had a history of allergy to components of the vaccine(s). No concomitant vaccines were permitted during study participation. *[See Adverse Reactions (6.1) for ethnicity and gender information.]*

A summary of antibody responses to measles, mumps, rubella, and varicella at 6 weeks postvaccination in subjects who had previously received M-M-R II and VARIVAX is shown in Table 12. Results from this study showed that a first dose of ProQuad after primary vaccination with M-M-R II and VARIVAX elicited a positive antibody response to all four antigens in greater than 98% of subjects. Post-vaccination GMTs for recipients of ProQuad were similar to those following a second dose of M-M-R II and VARIVAX administered concomitantly at separate injection sites (the lower bound of the 95% CI around the fold difference in measles, mumps, rubella, and varicella GMTs excluded 0.5). Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of M-M-R II given concomitantly with placebo (the lower bound of the 95% CI around the fold difference for the comparison of measles, mumps, and rubella GMTs excluded 0.5).

Table 12: Summary of Antibody Responses to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination in Subjects 4 to 6 Years of Age Who Had Previously Received M-M-R II and VARIVAX (Per-Protocol Population)

Group Number (Description)	n	GMT (95% CI)	Seropositivity Rate (95% CI)	% ≥4-Fold Rise in Titer (95% CI)	Geometric Mean Fold Rise (95% CI)
		Measles*			
Group 1 (N=399) (ProQuad + placebo)	367	1985.9 (1817.6, 2169.9)	100% (99.0%, 100%)	4.9% (2.9%, 7.6%)	1.21 (1.13, 1.30)
Group 2 (N=205) (M-M-R II + placebo)	185	2046.9 (1815.2, 2308.2)	100% (98.0%, 100%)	4.3% (1.9%, 8.3%)	1.28 (1.17, 1.40)
Group 3 (N=195) (M-M-R II + VARIVAX)	171	2084.3 (1852.3, 2345.5)	99.4% (96.8%, 100%)	4.7% (2.0%, 9.0%)	1.31 (1.17, 1.46)
		Mumps†			

Group 1 (N=399) (ProQuad + placebo)	367	206.0 (188.2, 225.4)	99.5% (98.0%, 99.9%)	27.2% (22.8%, 32.1%)	2.43 (2.19, 2.69)
Group 2 (N=205) (M-M-R II + placebo)	185	308.5 (269.6, 352.9)	100% (98.0%, 100%)	41.1% (33.9%, 48.5%)	3.69 (3.14, 4.32)
Group 3 (N=195) (M-M-R II + VARIVAX)	171	295.9 (262.5, 333.5)	100% (97.9%, 100%)	41.5% (34.0%, 49.3%)	3.36 (2.84, 3.97)
		Rubella[‡]			
Group 1 (N=399) (ProQuad + placebo)	367	217.3 (200.1, 236.0)	100% (99.0%, 100%)	32.7% (27.9%, 37.8%)	3.00 (2.72, 3.31)
Group 2 (N=205) (M-M-R II + placebo)	185	174.0 (157.3, 192.6)	100% (98.0%, 100%)	31.9% (25.2%, 39.1%)	2.81 (2.41, 3.27)
Group 3 (N=195) (M-M-R II + VARIVAX)	171	154.1 (138.9, 170.9)	99.4% (96.8%, 100%)	26.9% (20.4%, 34.2%)	2.47 (2.17, 2.81)
		Varicella[§]			
Group 1 (N=399) (ProQuad + placebo)	367	322.2 (278.9, 372.2)	98.9% (97.2%, 99.7%)	80.7 (76.2%, 84.6%)	12.43 (10.63, 14.53)
Group 2 (N=205) (M-M-R II + placebo)	185	N/A	N/A	N/A	N/A
Group 3 (N=195) (M-M-R II + VARIVAX)	171	209.3 (171.2, 255.9)	99.4% (96.8%, 100%)	71.9% (64.6%, 78.5%)	8.50 (6.69, 10.81)

[*] Measles GMTs are reported in mIU/mL; seropositivity corresponds to ≥120 mIU/mL.
[†] Mumps GMTs are reported in mumps Ab units/mL; seropositivity corresponds to ≥10 Ab units/mL.
[‡] Rubella titers obtained by the legacy format were converted to their corresponding titers in the modified format. Rubella serostatus was determined after the conversion to IU/mL: seropositivity corresponds to ≥10 IU/mL.
[§] Varicella GMTs are reported in gpELISA units/mL; seropositivity rate is reported by % of subjects with postvaccination antibody titers ≥5 gpELISA units/mL. Percentages are calculated as the number of subjects who met the criterion divided by the number of subjects contributing to the per-protocol analysis.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay; ELISA = Enzyme-linked immunosorbent assay; CI = Confidence interval; GMT = Geometric mean titer; N/A = Not applicable; N = Number of subjects vaccinated; n = number of subjects in the per-protocol analysis.

Immunogenicity Following Concomitant Use with Other Vaccines

ProQuad with Pneumococcal 7-valent Conjugate Vaccine and/or VAQTA

In a clinical trial, 1027 healthy children 12 to 15 months of age were randomized to receive ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly (N=510) at separate injection sites or ProQuad and pneumococcal 7-valent conjugate vaccine non-concomitantly (N=517) at separate clinic visits. *[See Adverse Reactions (6.1) for ethnicity and gender information.]* The statistical analysis of non-inferiority in antibody response rates to measles, mumps, rubella, and varicella at 6 weeks postvaccination for subjects are shown in Table 13. In the per-protocol population, seroconversion rates were not inferior in children given ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly when compared to seroconversion rates seen in children given these vaccines non-concomitantly for measles, mumps, and rubella. In children with baseline varicella antibody titers <1.25 gpELISA units/mL, the varicella seroprotection rates were not inferior when rates after concomitant and non-concomitant vaccination were compared 6 weeks postvaccination. Statistical analysis of non-inferiority in GMTs to *S. pneumoniae* serotypes at 6 weeks postvaccination are shown in Table 14. Geometric mean antibody titers (GMTs) for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were not inferior when antibody titers in the concomitant and non-concomitant groups were compared 6 weeks postvaccination.

Table 13: Statistical Analysis of Non-Inferiority in Antibody Response Rates to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or With Varicella Antibody Titer <1.25 gpELISA units at Baseline in the ProQuad + PCV7* Treatment Group and the ProQuad Followed by PCV7 Control Group (Per-Protocol Analysis)

Assay Parameter	ProQuad + PCV7 (N=510)		ProQuad followed by PCV7 (N=259)		Difference (percentage points)[†,‡] (95% CI)
	n	Estimated Response[†]	n	Estimated Response[†]	
Measles					
% ≥255 mIU/mL	406	97.3%	204	99.5%	-2.2 (-4.6, 0.2)
Mumps					

% ≥10 Ab units/mL	403	96.6%	208	98.6%	-1.9 (-4.5, 1.0)
Rubella % ≥10 IU/mL	377	98.7%	195	97.9%	0.9 (-1.3, 4.1)
Varicella % ≥5 gpELISA units/mL	379	92.5%	192	87.9%	4.5 (-0.4, 10.4)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
Seronegative defined as baseline measles antibody titer <255 mIU/mL for measles, baseline mumps antibody titer <10 ELISA Ab units/mL for mumps, and baseline rubella antibody titer <10 IU/mL for rubella.
† Estimated responses and their differences were based on statistical analysis models adjusting for study center.
‡ ProQuad + PCV7 - ProQuad followed by PCV7.
The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.*, excluding a decrease equal to or more than the prespecified criterion of 10.0 percentage points). This indicates that the difference is statistically significantly less than the prespecified clinically relevant decrease of 10.0 percentage points at the 1-sided alpha = 0.025 level.
N = Number of subjects vaccinated in each treatment group.
n = Number of subjects with measles antibody titer <255 mIU/mL, mumps antibody titer <10 ELISA Ab units/mL, rubella antibody titer <10 IU/mL, or varicella antibody titer <1.25 gpELISA units/mL at baseline and with postvaccination serology contributing to the per-protocol analysis.
Ab = antibody; ELISA = Enzyme-linked immunosorbent assay; gpELISA = Glycoprotein enzyme-linked immunosorbent assay; CI = Confidence interval.

Table 14: Statistical Analysis of Non-Inferiority in GMTs to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination in the ProQuad + PCV7* Treatment Group and the PCV7 Followed by ProQuad Control Group (Per-Protocol Analysis)

		Group 1 ProQuad + PCV7 (N=510)		Group 2 PCV7 followed by ProQuad (N=258)		
Serotype	Parameter	n	Estimated Response†	n	Estimated Response†	Fold-Difference*‡ (95% CI)
4	GMT	410	1.5	193	1.3	1.2 (1.0, 1.4)
6B	GMT	410	8.9	192	8.4	1.1 (0.9, 1.2)
9V	GMT	409	2.9	193	2.5	1.2 (1.0, 1.3)
14	GMT	408	6.5	193	5.7	1.1 (1.0, 1.3)
18C	GMT	408	2.3	193	2.0	1.2 (1.0, 1.3)
19F	GMT	408	3.5	192	3.1	1.1 (1.0, 1.3)
23F	GMT	413	4.1	197	3.7	1.1 (1.0, 1.3)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
† Estimated responses and their fold-difference were based on statistical analysis models adjusting for study center and prevaccination titer.
‡ ProQuad + PCV7 / PCV7 followed by ProQuad.
The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5, (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.
N = Number of subjects vaccinated in each treatment group; n = Number of subjects contributing to the per-protocol analysis for the given serotype; GMT = geometric mean titer; CI = Confidence interval.

In a clinical trial, 653 healthy children 12 to 15 months of age were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later (N=323). *[See Adverse Reactions (6.1) for ethnicity and gender information.]* Statistical analysis of non-inferiority of the response rate for varicella antibody at 6 weeks postvaccination among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 15. For the varicella component of ProQuad, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥5 gpELISA units/mL 6 weeks after their first dose of ProQuad was non-inferior when ProQuad was administered with VAQTA and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥5 gpELISA units/mL when ProQuad was administered with pneumococcal 7-valent conjugate vaccine alone. Statistical analysis of non-inferiority of the seropositivity rate for hepatitis A antibody at 4 weeks postdose 2 of VAQTA among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 16. The seropositivity rate to hepatitis A 4 weeks after a second dose of VAQTA given concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine (defined as the percent of subjects with a titer ≥10 mIU/mL) was non-inferior to the seropositivity rate

observed when VAQTA was administered separately from ProQuad and pneumococcal 7-valent conjugate vaccine. Statistical analysis of non-inferiority in GMT to *S. pneumoniae* serotypes at 6 weeks postvaccination among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 17. Additionally, the GMTs for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad and VAQTA were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent conjugate vaccine with ProQuad alone. An earlier clinical study involving 617 healthy children provided data that indicated that the seroresponse rates 6 weeks post vaccination for measles, mumps, and rubella in those given M-M-R II and VAQTA concomitantly (N=309) were non-inferior as compared to historical controls.

Table 15: Statistical Analysis of Non-Inferiority of the Response Rate for Varicella Antibody at 6 Weeks Postvaccination Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)

Parameter	Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)		Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)		Difference† (percentage points): Group 1 – Group 2 (95% CI)
	n	Estimated Response†	n	Estimated Response†	
% ≥5 gpELISA units/mL‡	225§	93.2%	232§	98.3%	-5.1 (-9.3, -1.4)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for varicella; CI = Confidence interval.
† Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.
‡ 6 weeks following Dose 1.
§ Initial Serostatus <1.25 gpELISA units/ mL.
The conclusion of similarity (non-inferiority) was based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease of 10 percentage points or more (lower bound >-10.0). This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

Table 16: Statistical Analysis of Non-Inferiority of the Seropositivity Rate (SPR) for Hepatitis A Antibody at 4 Weeks Postdose 2 of VAQTA Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)

Parameter	Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)		Group 2: Non-concomitant VAQTA separate from ProQuad + PCV7 (N=323)		Difference† (percentage points): Group 1 - Group 2 (95% CI)
	n	Estimated Response†	n	Estimated Response†	
% ≥10 mIU/mL‡	182§	100.0%	159§	99.3%	0.7 (-1.4, 3.8)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
CI = Confidence interval; N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for hepatitis A.
† Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.
‡ 4 weeks following receipt of 2 doses of VAQTA.
§ Regardless of initial serostatus.
The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.*, excluding a decrease of 10 percentage points or more) (lower bound >-10.0). This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

Table 17: Statistical Analysis of Non-Inferiority in Geometric Mean Titers (GMT) to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)

	Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330)	Group 2: Non-concomitant VAQTA separate from

Serotype			ProQuad + PCV7 (N=323)		Fold-Difference† (95% CI)
	n	Estimated Response†	n	Estimated Response†	
4	246	1.9	247	1.7	1.1 (0.9, 1.3)
6B	246	9.9	246	9.9	1.0 (0.8, 1.2)
9V	247	3.7	247	4.2	0.9 (0.8, 1.0)
14	248	7.8	247	7.6	1.0 (0.9, 1.2)
18C	247	2.9	247	2.7	1.1 (0.9, 1.3)
19F	248	4.0	248	3.8	1.1 (0.9, 1.2)
23F	247	5.1	247	4.4	1.1 (1.0, 1.3)

* PCV7 = Pneumococcal 7-valent conjugate vaccine.
CI = Confidence interval; GMT = Geometric mean titer; N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for *S. pneumoniae* serotypes.
† Estimated responses and their fold-difference were based on statistical analysis models adjusting for combined study center and prevaccination titer.
The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5 (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference was statistically significantly less than the prespecified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.

ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine

In a clinical trial, 1913 healthy children 12 to 15 months of age were randomized to receive ProQuad plus diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly at separate injection sites (N=949), ProQuad at the initial visit followed by DTaP and *Haemophilus* b conjugate and hepatitis B (recombinant) vaccine given concomitantly 6 weeks later (N=485), or M-M-R II and VARIVAX given concomitantly at separate injection sites (N=479) at the first visit. *[See Adverse Reactions (6.1) for ethnicity and gender information.]* Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, anti-PRP, and hepatitis B were comparable between the 2 groups given ProQuad at approximately 6 weeks postvaccination indicating that ProQuad and *Haemophilus* b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine may be administered concomitantly at separate injection sites (see Table 18 below). Response rates for measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, and hepatitis B were not inferior in children given ProQuad plus *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines concomitantly when compared to ProQuad at the initial visit and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines given concomitantly 6 weeks later. There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (data not shown).

Table 18: Summary of the Comparison of the Immunogenicity Endpoints for Measles, Mumps, Rubella, Varicella, *Haemophilus influenzae* type b, and Hepatitis B Responses Following Vaccination with ProQuad, *Haemophilus influenzae* type b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine and DTaP Administered Concomitantly Versus Non-Concomitant Vaccination with ProQuad Followed by These Vaccines

		Concomitant Group	Non-Concomitant Group		
		N=949	N=485		
Vaccine Antigen	Parameter	Response	Response	Risk Difference (95% CI)	Criterion for Non-inferiority
Measles	% ≥120 mIU/mL	97.8%	98.7%	-0.9 (-2.3, 0.6)	LB >-5.0
Mumps	% ≥10 ELISA Ab units/mL	95.4%	95.1%	0.3 (-1.7, 2.6)	LB >-5.0
Rubella	% ≥10 IU/mL	98.6%	99.3%	-0.7 (-1.8, 0.5)	LB >-5.0
Varicella	% ≥5 gpELISA	89.6%	90.8%	-1.2	LB >-10.0

	units/mL			(-4.1, 2.0)	
HIB-PRP	% ≥1.0 mcg/mL	94.6%	96.5%	-1.9 (-4.1, 0.8)	LB >-10.0
HepB	% ≥10 mIU/mL	95.9%	98.8%	-2.8 (-4.8, -0.8)	LB >10.0

HIB-PRP = *Haemophilus influenzae* type b, polyribosyl phosphate; HepB = hepatitis B; LB = lower bound, limit for non-inferiority comparison.

15 REFERENCES

1. Levy O, et al. Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells. *J Infect Dis*. 188(7):948-53, 2003.
2. Committee on Infectious Diseases, American Academy of Pediatrics. In: Pickering LK, Baker CJ, Overturf GD, et al., eds. Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics. 419-29, 2003.
3. Peltola H, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med*. 331(21):1397-1402, 1994.
4. Bennetto L, Scolding N. Inflammatory/post-infectious encephalomyelitis. *J Neurol Neurosurg Psychiatry* 2004;75(Suppl 1):i22-8.
5. Fenichel GM. Neurological complications of immunization. *AnnNeurol* 1982;12(2):119-28.
6. Guess HA, et al. Population-based studies of varicella complications. *Pediatrics*. 78(4 Pt 2):723-727, 1986.
7. Recommendations of the Immunization Practices Advisory Committee (ACIP), Mumps Prevention. *MMWR*. 38(22):388-392, 397-400, 1989.
8. Rubella vaccination during pregnancy--United States, 1971-1986. *MMWR Morb Mortal Wkly Rep*. 36(28):457-61, 1987.
9. Bohlke K, Galil K, Jackson LA, et al. Postpartum varicella vaccination: Is the vaccine virus excreted in breast milk? *Obstetrics and Gynecology*. 102(5):970-977, 2003.
10. Dolbear GL, Moffat J, Falkner C and Wojtowycz M. A Pilot Study: Is attenuated varicella virus present in breast milk after postpartum immunization? *Obstetrics and Gynecology*. 101(4 Suppl.):47S-47S, 2003.
11. Weibel RE, et al. Clinical and laboratory studies of combined live measles, mumps, and rubella vaccines using the RA 27/3 rubella virus. *Proc Soc Exp Biol Med*. 165(2):323-326, 1980.
12. Hilleman MR, Stokes J, Jr., Buynak EB, Weibel R, Halenda R, Goldner H. Studies of live attenuated measles virus vaccine in man: II. appraisal of efficacy. *Am J Public Health*. 52(2):44-56, 1962.
13. Krugman S, Giles JP, Jacobs AM. Studies on an attenuated measles-virus vaccine: VI. clinical, antigenic and prophylactic effects of vaccine in institutionalized children. *N Engl J Med*. 263(4):174-7, 1960.
14. Hilleman MR, Weibel RE, Buynak EB, Stokes J, Jr., Whitman JE, Jr. Live, attenuated mumps-virus vaccine. 4. Protective efficacy as measured in a field evaluation. *N Engl J Med*. 276(5):252-8, 1967.
15. Sugg WC, Finger JA, Levine RH, Pagano JS. Field evaluation of live virus mumps vaccine. *J Pediatr*. 72(4):461-6, 1968.
16. The Benevento and Compobasso Pediatricians Network for the Control of Vaccine-Preventable Diseases, D'Argenio P, Citarella A, Selvaggi MTM. Field evaluation of the clinical effectiveness of vaccines against pertussis, measles, rubella and mumps. *Vaccine*. 16(8):818-22, 1998.
17. Furukawa T, Miyata T, Kondo K, Kuno K, Isomura S, Takekoshi T. Rubella vaccination during an epidemic. *JAMA*. 213(6):987-90, 1970.
18. Vazquez M, et al. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med*. 344(13):955-960, 2001.
19. Kuter B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J*. 23(2):132-137, 2004.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4999 — ProQuad is supplied as follows:
(1) a package of 10 single-dose vials of lyophilized vaccine, NDC 0006-4999-00 (package A)
(2) a separate package of 10 vials of sterile water diluent (package B).

Storage

To maintain potency, ProQuad must be stored frozen between -58°F and +5°F (-50°C to -15°C). Use of dry ice may subject ProQuad to temperatures colder than -58°F (-50°C).

Before reconstitution, store the lyophilized vaccine continuously in a reliably maintained freezer (*e.g.*, chest, frost-free) for up to 18 months.

ProQuad may be stored at refrigerator temperature (36° to 46°F, 2° to 8°C) for up to 72 hours prior to reconstitution. Discard any ProQuad vaccine stored at 36° to 46°F which is not used within 72 hours of removal from 5°F (-15°C) storage.

Protect the vaccine from light at all times since such exposure may inactivate the vaccine viruses.

IF NOT USED IMMEDIATELY, THE RECONSTITUTED VACCINE MAY BE STORED AT ROOM TEMPERATURE, PROTECTED FROM LIGHT, FOR UP TO 30 MINUTES.

DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

DO NOT FREEZE RECONSTITUTED VACCINE.

Diluent should be stored separately at room temperature (68° to 77°F, 20° to 25°C), or in a refrigerator (36° to 46°F, 2° to 8°C).

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

17 PATIENT COUNSELING INFORMATION

Instructions

Provide the required vaccine information to the patient, parent, or guardian.

Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.

Inform the patient, parent, or guardian that the vaccine recipient should avoid use of salicylates for 6 weeks after vaccination with ProQuad *[see Adverse Reactions (6.1) and Drug Interactions (7.2)]*.

Instruct postpubertal females to avoid pregnancy for 3 months following vaccination *[see Indications and Usage (1) and Use In Specific Populations (8.1)]*.

Inform patients, parents, or guardians that vaccination with ProQuad may not offer 100% protection from measles, mumps, rubella, and varicella infection.

Instruct patients, parents, or guardians to report any adverse reactions to their health care provider. The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at http://www.vaers.hhs.gov.

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MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-v221-i-fro-hsa-1510r910

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VARIVAX safely and effectively. See full prescribing information for VARIVAX.

VARIVAX®
Varicella Virus Vaccine Live
Suspension for subcutaneous injection
Initial U.S. Approval: 1995

INDICATIONS AND USAGE

VARIVAX is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older. (1)

DOSAGE AND ADMINISTRATION

Each dose is approximately 0.5 mL after reconstitution and is administered by subcutaneous injection. (2.1)

Children (12 months to 12 years of age)

- If a second dose is administered, there should be a minimum interval of 3 months between doses. (2.1)

Adolescents (≥13 years of age) and Adults

- Two doses, to be administered a minimum of 4 weeks apart. (2.1)

DOSAGE FORMS AND STRENGTHS

Suspension for injection (approximately 0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using the accompanying sterile diluent. (2.2, 3, 16)

CONTRAINDICATIONS

- History of severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of varicella vaccine. (4.1)
- Primary or acquired immunodeficiency states. (4.2)
- Any febrile illness or active infection, including untreated tuberculosis. (4.3)
- Pregnancy. (4.4, 8.1, 17)

WARNINGS AND PRECAUTIONS

- Evaluate individuals for immune competence prior to administration of VARIVAX if there is a family history of congenital or hereditary immunodeficiency. (5.2)
- Avoid contact with high-risk individuals susceptible to varicella because of possible transmission of varicella vaccine virus. (5.4)
- Defer vaccination for at least 5 months following blood or plasma transfusions, or administration of immune globulins (IG). (5.5, 7.2)
- Avoid use of salicylates for 6 weeks following administration of VARIVAX to children and adolescents. (5.6, 7.1)

ADVERSE REACTIONS

- Frequently reported (≥10%) adverse reactions in children ages 1 to 12 years include:
  - fever ≥102.0°F (38.9°C) oral: 14.7%
  - injection-site complaints: 19.3% (6.1)
- Frequently reported (≥10%) adverse reactions in adolescents and adults ages 13 years and older include:
  - fever ≥100.0°F (37.8°C) oral: 10.2%
  - injection-site complaints: 24.4% (6.1)
- Other reported adverse reactions in all age groups include:
  - varicella-like rash (injection site)
  - varicella-like rash (generalized) (6.1)

To report SUSPECTED ADVERSE REACTIONS or exposure during pregnancy or within three months prior to conception, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

- Reye syndrome has been reported in children and adolescents following the use of salicylates during wild-type varicella infection. (5.6, 7.1)
- Passively acquired antibodies from blood, plasma, or immunoglobulin potentially may inhibit the response to varicella vaccination. (5.5, 7.2)
- Tuberculin skin testing may be performed before VARIVAX is administered or on the same day, or six weeks following vaccination with VARIVAX. (7.3)

USE IN SPECIFIC POPULATIONS

Pregnancy: Do not administer VARIVAX to females who are pregnant; the possible effects of the vaccine on fetal development are unknown. Pregnancy should be avoided for 3 months following vaccination with VARIVAX. (4.4, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VARIVAX® is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION

Subcutaneous administration only

2.1 Recommended Dose and Schedule

VARIVAX is administered as an approximately 0.5-mL dose by subcutaneous injection into the outer aspect of the upper arm (deltoid region) or the anterolateral thigh.

Do not administer this product intravascularly or intramuscularly.

Children (12 months to 12 years of age)

If a second dose is administered, there should be a minimum interval of 3 months between doses *[see Clinical Studies (14.1)]*.

Adolescents (≥13 years of age) and Adults

Two doses of vaccine, to be administered with a minimum interval of 4 weeks between doses *[see Clinical Studies (14.1)]*.

2.2 Reconstitution Instructions

When reconstituting the vaccine, use only the sterile diluent supplied with VARIVAX. The sterile diluent does not contain preservatives or other anti-viral substances which might inactivate the vaccine virus.

Use a sterile syringe free of preservatives, antiseptics, and detergents for each reconstitution and injection of VARIVAX because these substances may inactivate the vaccine virus.

To reconstitute the vaccine, first withdraw the total volume of provided sterile diluent into a syringe. Inject all of the withdrawn diluent into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into the syringe and inject the total volume (approximately 0.5 mL) of reconstituted vaccine subcutaneously. VARIVAX, when reconstituted, is a clear, colorless to pale yellow liquid.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored.

To minimize loss of potency, administer VARIVAX immediately after reconstitution. Discard if reconstituted vaccine is not used within 30 minutes.

Do not freeze reconstituted vaccine.

Do not combine VARIVAX with any other vaccine through reconstitution or mixing.

3 DOSAGE FORMS AND STRENGTHS

VARIVAX is a suspension for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent *[see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]*. A single dose after reconstitution is approximately 0.5 mL.

4 CONTRAINDICATIONS

4.1 Severe Allergic Reaction

Do not administer VARIVAX to individuals with a history of anaphylactic or severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of a varicella-containing vaccine.

4.2 Immunosuppression

Do not administer VARIVAX to immunosuppressed or immunodeficient individuals, including those with a history of primary or acquired immunodeficiency states, leukemia, lymphoma or other malignant

neoplasms affecting the bone marrow or lymphatic system, AIDS, or other clinical manifestations of infection with human immunodeficiency virus (HIV).

Do not administer VARIVAX to individuals receiving immunosuppressive therapy, including individuals receiving immunosuppressive doses of corticosteroids.

VARIVAX is a live, attenuated varicella-zoster vaccine (VZV) and may cause an extensive vaccine-associated rash or disseminated disease in individuals who are immunosuppressed or immunodeficient.

4.3 Concurrent Illness

Do not administer VARIVAX to individuals with any febrile illness. Do not administer VARIVAX to individuals with active, untreated tuberculosis.

4.4 Pregnancy

Do not administer VARIVAX to individuals who are pregnant because the effects of the vaccine on fetal development are unknown. Wild-type varicella (natural infection) is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should anaphylaxis occur.

5.2 Family History of Immunodeficiency

Vaccination should be deferred in patients with a family history of congenital or hereditary immunodeficiency until the patient's immune status has been evaluated and the patient has been found to be immunocompetent.

5.3 Use in HIV-Infected Individuals

The Advisory Committee for Immunization Practices (ACIP) has recommendations on the use of varicella vaccine in HIV-infected individuals.

5.4 Risk of Vaccine Virus Transmission

Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from a mother who did not develop a varicella-like rash to her newborn infant has been reported.

Due to the concern for transmission of vaccine virus, vaccine recipients should attempt to avoid whenever possible close association with susceptible high-risk individuals for up to six weeks following vaccination with VARIVAX. Susceptible high-risk individuals include:

- Immunocompromised individuals;
- Pregnant women without documented history of varicella or laboratory evidence of prior infection;
- Newborn infants of mothers without documented history of varicella or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

5.5 Immune Globulins and Transfusions

Immunoglobulins should not be given concomitantly with VARIVAX. Vaccination should be deferred for at least 5 months following blood or plasma transfusions, or administration of immune globulin(s) {1}.

Following administration of VARIVAX, immune globulin(s) should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination {1}. *[See Drug Interactions (7.2).]*

5.6 Salicylate Therapy

Avoid use of salicylates (aspirin) or salicylate-containing products in children and adolescents 12 months through 17 years of age for six weeks following vaccination with VARIVAX because of the association of Reye syndrome with aspirin therapy and wild-type varicella infection. *[See Drug Interactions (7.1).]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

In clinical trials {2-9}, VARIVAX was administered to over 11,000 healthy children, adolescents, and adults.

In a double-blind, placebo-controlled study among 914 healthy children and adolescents who were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at a significantly ($p<0.05$) greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site {2}.

Children 1 to 12 Years of Age

One-Dose Regimen in Children

In clinical trials involving healthy children monitored for up to 42 days after a single dose of VARIVAX, the frequency of fever, injection-site complaints, or rashes were reported as shown in Table 1:

Table 1: Fever, Local Reactions, and Rashes (%) in Children 1 to 12 Years of Age 0 to 42 Days After Receipt of a Single Dose of VARIVAX

Reaction	N	% Experiencing Reaction	Peak Occurrence During Postvaccination Days
Fever ≥102.0°F (38.9°C) Oral	8827	14.7%	0 to 42
Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness)	8916	19.3%	0 to 2
Varicella-like rash (injection site) Median number of lesions	8916	3.4% 2	8 to 19
Varicella-like rash (generalized) Median number of lesions	8916	3.8% 5	5 to 26

In addition, adverse events occurring at a rate of ≥1% are listed in decreasing order of frequency: upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, diaper rash/contact rash, headache, teething, malaise, abdominal pain, other rash, nausea, eye complaints, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, heat rash/prickly heat, arthralgia, eczema/dry skin/dermatitis, constipation, itching.

Pneumonitis has been reported rarely (<1%) in children vaccinated with VARIVAX.

Febrile seizures have occurred at a rate of <0.1% in children vaccinated with VARIVAX.

Two-Dose Regimen in Children

Nine hundred eighty-one (981) subjects in a clinical trial received 2 doses of VARIVAX 3 months apart and were actively followed for 42 days after each dose. The 2-dose regimen of varicella vaccine had a safety profile comparable to that of the 1-dose regimen. The overall incidence of injection-site clinical complaints (primarily erythema and swelling) observed in the first 4 days following vaccination was 25.4% Postdose 2 and 21.7% Postdose 1, whereas the overall incidence of systemic clinical complaints in the 42-day follow-up period was lower Postdose 2 (66.3%) than Postdose 1 (85.8%).

Adolescents (13 Years of Age and Older) and Adults

In clinical trials involving healthy adolescents and adults, the majority of whom received two doses of VARIVAX and were monitored for up to 42 days after any dose, the frequencies of fever, injection-site complaints, or rashes are shown in Table 2.

Table 2: Fever, Local Reactions, and Rashes (%) in Adolescents and Adults 0 to 42 Days After Receipt of VARIVAX

Reaction	N	% Post Dose 1	Peak Occurrence in Postvaccination Days	N	% Post Dose 2	Peak Occurrence in Postvaccination Days
Fever ≥100.0°F (37.8°C) Oral	1584	10.2%	14 to 27	956	9.5%	0 to 42
Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness)	1606	24.4%	0 to 2	955	32.5%	0 to 2
Varicella-like rash (injection site) Median number of lesions	1606	3% 2	6 to 20	955	1% 2	0 to 6
Varicella-like rash (generalized) Median number of lesions	1606	5.5% 5	7 to 21	955	0.9% 5.5	0 to 23

In addition, adverse events reported at a rate of ≥1% are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, diarrhea, stiff neck, irritability/nervousness, lymphadenopathy, chills, eye complaints, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, constipation, lower respiratory illness, allergic reactions (including allergic rash, hives), contact rash, cold/canker sore.

6.2 Post-Marketing Experience

Broad use of VARIVAX could reveal adverse events not observed in clinical trials.

The following additional adverse events, regardless of causality, have been reported during post-marketing use of VARIVAX:

Body as a Whole

Anaphylaxis (including anaphylactic shock) and related phenomena such as angioneurotic edema, facial edema, and peripheral edema.

Eye Disorders

Necrotizing retinitis (in immunocompromised individuals).

Hemic and Lymphatic System

Aplastic anemia; thrombocytopenia (including idiopathic thrombocytopenic purpura (ITP)).

Infections and Infestations

Varicella (vaccine strain).

Nervous/Psychiatric

Encephalitis; cerebrovascular accident; transverse myelitis; Guillain-Barré syndrome; Bell's palsy; ataxia; non-febrile seizures; aseptic meningitis; dizziness; paresthesia.

Respiratory

Pharyngitis; pneumonia/pneumonitis.

Skin

Stevens-Johnson syndrome; erythema multiforme; Henoch-Schönlein purpura; secondary bacterial infections of skin and soft tissue, including impetigo and cellulitis; herpes zoster.

7 DRUG INTERACTIONS

7.1 Salicylates

No cases of Reye syndrome have been observed following vaccination with VARIVAX. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX, as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection *[see Warnings and Precautions (5.6)]*.

7.2 Immune Globulins and Transfusions

Blood, plasma, and immune globulins contain antibodies that may interfere with vaccine virus replication and decrease the immune response to VARIVAX. Vaccination should be deferred for at least 5 months following blood or plasma transfusions, or administration of immune globulin(s) {1}.

Following administration of VARIVAX, immune globulin(s) should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination {1}. *[See Warnings and Precautions (5.5).]*

7.3 Tuberculin Skin Testing

Tuberculin skin testing, with tuberculin purified protein derivative (PPD), may be performed before VARIVAX is administered or on the same day, or at least 4 weeks following vaccination with VARIVAX, as other live virus vaccines may cause a temporary depression of tuberculin skin test sensitivity leading to false negative results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category: Contraindication *[see Contraindications (4.4)]*. VARIVAX should not be administered to pregnant females since wild-type varicella can sometimes cause congenital varicella infection. Pregnancy should be avoided for three months following vaccination with VARIVAX *[see Contraindications (4.4) and Patient Counseling Information (17)]*.

Pregnancy Registry

From 1995 to 2013, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintained a Pregnancy Registry to monitor fetal outcomes following inadvertent administration of VARIVAX during pregnancy or within three months prior to conception. In 2006, reports of exposure to two other varicella (Oka/Merck)-containing vaccines, ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) and ZOSTAVAX® (Zoster Vaccine Live), were added to the Registry. The Pregnancy Registry has been discontinued. As of March 2011, 811 women with pregnancy outcome information available for analysis were prospectively enrolled following vaccination with VARIVAX, within three months prior to conception or any time during pregnancy. Of these women, 170 were seronegative at the time of exposure and 627 women had an unknown serostatus. The remaining women were seropositive. Nine exposures to either ProQuad or ZOSTAVAX have been reported that met criteria for inclusion into the Registry.

None of the 820 women who received a varicella-containing vaccine delivered infants with abnormalities consistent with congenital varicella syndrome.

All exposures to VARIVAX, ProQuad, or ZOSTAVAX during pregnancy or within three months prior to conception should be reported as suspected adverse reactions by contacting Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

8.3 Nursing Mothers

It is not known whether varicella vaccine virus is excreted in human milk. Therefore, because some viruses are excreted in human milk, caution should be exercised if VARIVAX is administered to a nursing woman. *[See Warnings and Precautions (5.4).]*

8.4 Pediatric Use

No clinical data are available on safety or efficacy of VARIVAX in children less than 12 months of age.

8.5 Geriatric Use

Clinical studies of VARIVAX did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

VARIVAX [Varicella Virus Vaccine Live] is a preparation of the Oka/Merck strain of live, attenuated varicella virus. The virus was initially obtained from a child with wild-type varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus for varicella vaccine was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were free of adventitious agents. This live, attenuated varicella vaccine is a lyophilized preparation containing sucrose, phosphate, glutamate, and processed gelatin as stabilizers.

VARIVAX, when reconstituted as directed, is a sterile preparation for subcutaneous injection. Each approximately 0.5-mL dose contains a minimum of 1350 plaque-forming units (PFU) of Oka/Merck varicella virus when reconstituted and stored at room temperature for a maximum of 30 minutes. Each 0.5-mL dose also contains approximately 25 mg of sucrose, 12.5 mg hydrolyzed gelatin, 3.2 mg of sodium chloride, 0.5 mg of monosodium L-glutamate, 0.45 mg of sodium phosphate dibasic, 0.08 mg of potassium phosphate monobasic, and 0.08 mg of potassium chloride. The product also contains residual

components of MRC-5 cells including DNA and protein and trace quantities of sodium phosphate monobasic, EDTA, neomycin and fetal bovine serum. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VARIVAX induces both cell-mediated and humoral immune responses to varicella-zoster virus. The relative contributions of humoral immunity and cell-mediated immunity to protection from varicella are unknown.

12.2 Pharmacodynamics

Transmission

In the placebo-controlled efficacy trial, transmission of vaccine virus was assessed in household settings (during the 8-week postvaccination period) in 416 susceptible placebo recipients who were household contacts of 445 vaccine recipients. Of the 416 placebo recipients, three developed varicella and seroconverted, nine reported a varicella-like rash and did not seroconvert, and six had no rash but seroconverted. If vaccine virus transmission occurred, it did so at a very low rate and possibly without recognizable clinical disease in contacts. These cases may represent either wild-type varicella from community contacts or a low incidence of transmission of vaccine virus from vaccinated contacts *[see Warnings and Precautions (5.4)]* {2,10}. Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from a mother who did not develop a varicella-like rash to her newborn infant has also been reported.

Herpes Zoster

Overall, 9454 healthy children (12 months to 12 years of age) and 1648 adolescents and adults (13 years of age and older) have been vaccinated with VARIVAX in clinical trials. Eight cases of herpes zoster have been reported in children during 42,556 person-years of follow-up in clinical trials, resulting in a calculated incidence of at least 18.8 cases per 100,000 person-years. The completeness of this reporting has not been determined. One case of herpes zoster has been reported in the adolescent and adult age group during 5410 person-years of follow-up in clinical trials, resulting in a calculated incidence of 18.5 cases per 100,000 person-years. All 9 cases were mild and without sequelae. Two cultures (one child and one adult) obtained from vesicles were positive for wild-type VZV as confirmed by restriction endonuclease analysis {11}. The long-term effect of VARIVAX on the incidence of herpes zoster, particularly in those vaccinees exposed to wild-type varicella, is unknown at present.

In children, the reported rate of herpes zoster in vaccine recipients appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella {12}. The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.

12.4 Duration of Protection

The duration of protection of VARIVAX is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination {13} *[see Clinical Studies (14.1)]*. A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella which could account for the apparent long-term protection after vaccination in these studies.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

The protective efficacy of VARIVAX was established by: (1) a placebo-controlled, double-blind clinical trial, (2) comparing varicella rates in vaccinees versus historical controls, and (3) assessing protection from disease following household exposure.

Clinical Data in Children

One-Dose Regimen in Children

Although no placebo-controlled trial was carried out with VARIVAX using the current vaccine, a placebo-controlled trial was conducted using a formulation containing 17,000 PFU per dose {2,14}. In this trial, a single dose of VARIVAX protected 96 to 100% of children against varicella over a two-year period. The study enrolled healthy individuals 1 to 14 years of age (n=491 vaccine, n=465 placebo). In the first year, 8.5% of placebo recipients contracted varicella, while no vaccine recipient did, for a calculated

protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n=163 vaccine, n=161 placebo), 96% protective efficacy was calculated for the vaccine group as compared to placebo.

In early clinical trials, a total of 4240 children 1 to 12 years of age received 1000 to 1625 PFU of attenuated virus per dose of VARIVAX and have been followed for up to nine years post single-dose vaccination. In this group there was considerable variation in varicella rates among studies and study sites, and much of the reported data were acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported varicella (called breakthrough cases). This represents an approximate 83% (95% confidence interval [CI], 82%, 84%) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period {12}. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease (median of the maximum number of lesions <50). In one study, a total of 47% (27/58) of breakthrough cases had <50 lesions compared with 8% (7/92) in unvaccinated individuals, and 7% (4/58) of breakthrough cases had >300 lesions compared with 50% (46/92) in unvaccinated individuals {15}.

Among a subset of vaccinees who were actively followed in these early trials for up to nine years postvaccination, 179 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 84% (150/179) of exposed children, while 16% (29/179) reported a mild form of varicella (38% [11/29] of the cases with a maximum total number of <50 lesions; no individuals with >300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

In later clinical trials, a total of 1114 children 1 to 12 years of age received 2900 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to 10 years post single-dose vaccination. It was observed that 0.2% to 2.3% of vaccinees per year reported breakthrough varicella for up to 10 years post single-dose vaccination. This represents an estimated efficacy of 94% (95% CI, 93%, 96%), compared with the age-adjusted expected incidence rates in susceptible subjects over the same period {2,12,16}. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease, with the median of the maximum total number of lesions <50. The severity of reported breakthrough varicella, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed in these later trials for up to 10 years postvaccination, 95 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella in 92% (87/95) of exposed children, while 8% (8/95) reported a mild form of varicella (maximum total number of lesions <50; observed range, 10 to 34). This represents an estimated efficacy of 90% (95% CI, 82%, 96%) based on the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

Two-Dose Regimen in Children

In a clinical trial, a total of 2216 children 12 months to 12 years of age with a negative history of varicella were randomized to receive either 1 dose of VARIVAX (n=1114) or 2 doses of VARIVAX (n=1102) given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness, or herpes zoster and any exposures to varicella or herpes zoster on an annual basis for 10 years after vaccination. Persistence of VZV antibody was measured annually for 9 years. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild {13}. The estimated vaccine efficacy for the 10-year observation period was 94% for 1 dose and 98% for 2 doses (p<0.001). This translates to a 3.4-fold lower risk of developing varicella >42 days postvaccination during the 10-year observation period in children who received 2 doses than in those who received 1 dose (2.2% vs. 7.5%, respectively).

Clinical Data in Adolescents and Adults

Two-Dose Regimen in Adolescents and Adults

In early clinical trials, a total of 796 adolescents and adults received 905 to 1230 PFU of attenuated virus per dose of VARIVAX and have been followed for up to six years following 2-dose vaccination. A total of 50 clinical varicella cases were reported >42 days following 2-dose vaccination. Based on passive follow-up, the annual varicella breakthrough event rate ranged from <0.1 to 1.9%. The median of the maximum total number of lesions ranged from 15 to 42 per year.

Although no placebo-controlled trial was carried out in adolescents and adults, the protective efficacy of VARIVAX was determined by evaluation of protection when vaccinees received 2 doses of VARIVAX 4 or 8 weeks apart and were subsequently exposed to varicella in a household setting. Among the subset of vaccinees who were actively followed in these early trials for up to six years, 76 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 83% (63/76) of exposed vaccinees, while 17% (13/76) reported a mild form of varicella. Among 13 vaccinated individuals who developed breakthrough varicella after a household exposure, 62% (8/13) of the cases reported maximum total number of lesions <50, while no individual reported >75 lesions. The attack rate of unvaccinated adults exposed to a single contact in a household has not been previously studied. Utilizing the previously reported historical attack rate of 87% for wild-type varicella following household exposure to varicella among unvaccinated children in the calculation of efficacy, this represents an approximate 80% reduction in the expected number of cases in the household setting.

In later clinical trials, a total of 220 adolescents and adults received 3315 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to six years following 2-dose vaccination. A total of 3 clinical varicella cases were reported >42 days following 2-dose vaccination. Two cases reported <50 lesions and none reported >75. The annual varicella breakthrough event rate ranged from 0 to 1.2%. Among the subset of vaccinees who were actively followed in these later trials for up to five years, 16 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella among the exposed vaccinees.

There are insufficient data to assess the rate of protective efficacy of VARIVAX against the serious complications of varicella in adults (*e.g.*, encephalitis, hepatitis, pneumonitis) and during pregnancy (congenital varicella syndrome).

14.2 Immunogenicity

In clinical trials, varicella antibodies have been evaluated following vaccination with formulations of VARIVAX containing attenuated virus ranging from 1000 to 50,000 PFU per dose in healthy individuals ranging from 12 months to 55 years of age {2,9}.

One-Dose Regimen in Children

In prelicensure efficacy studies, seroconversion was observed in 97% of vaccinees at approximately 4 to 6 weeks postvaccination in 6889 susceptible children 12 months to 12 years of age. Titers ≥5 gpELISA units/mL were induced in approximately 76% of children vaccinated with a single dose of vaccine at 1000 to 17,000 PFU per dose. Rates of breakthrough disease were significantly lower among children with VZV antibody titers ≥5 gpELISA units/mL compared with children with titers <5 gpELISA units/mL.

Two-Dose Regimen in Children

In a multicenter study, 2216 healthy children 12 months to 12 years of age received either 1 dose of VARIVAX or 2 doses administered 3 months apart. The immunogenicity results are shown in Table 3.

Table 3: Summary of VZV Antibody Responses at 6 Weeks Postdose 1 and 6 Weeks Postdose 2 in Initially Seronegative Children 12 Months to 12 Years of Age (Vaccinations 3 Months Apart)

	VARIVAX 1-Dose Regimen (N=1114)	VARIVAX 2-Dose Regimen (3 months apart) (N=1102)	
	6 Weeks Postvaccination (n=892)	6 Weeks Postdose 1 (n=851)	6 Weeks Postdose 2 (n=769)
Seroconversion Rate	98.9%	99.5%	99.9%
Percent with VZV Antibody Titer ≥5 gpELISA units/mL	84.9%	87.3%	98.5%
Geometric mean titers in gpELISA units/mL (95% CI)	12.0 (11.2, 12.8)	12.8 (11.9, 13.7)	141.5 (132.3, 151.3)

N = Number of subjects vaccinated.
n = Number of subjects included in immunogenicity analysis.

The results from this study and other studies in which a second dose of VARIVAX was administered 3 to 6 years after the initial dose demonstrate significant boosting of the VZV antibodies with a second dose. VZV antibody levels after 2 doses given 3 to 6 years apart are comparable to those obtained when the 2 doses are given 3 months apart.

Two-Dose Regimen in Adolescents and Adults

In a multicenter study involving susceptible adolescents and adults 13 years of age and older, 2 doses of VARIVAX administered 4 to 8 weeks apart induced a seroconversion rate of approximately 75% in 539 individuals 4 weeks after the first dose and of 99% in 479 individuals 4 weeks after the second dose. The average antibody response in vaccinees who received the second dose 8 weeks after the first dose was higher than that in vaccinees who received the second dose 4 weeks after the first dose. In another multicenter study involving adolescents and adults, 2 doses of VARIVAX administered 8 weeks apart induced a seroconversion rate of 94% in 142 individuals 6 weeks after the first dose and 99% in 122 individuals 6 weeks after the second dose.

14.3 Persistence of Immune Response

One-Dose Regimen in Children

In clinical studies involving healthy children who received 1 dose of vaccine, detectable VZV antibodies were present in 99.0% (3886/3926) at 1 year, 99.3% (1555/1566) at 2 years, 98.6% (1106/1122) at 3 years, 99.4% (1168/1175) at 4 years, 99.2% (737/743) at 5 years, 100% (142/142) at 6 years, 97.4% (38/39) at 7 years, 100% (34/34) at 8 years, and 100% (16/16) at 10 years postvaccination.

Two-Dose Regimen in Children

In recipients of 1 dose of VARIVAX over 9 years of follow-up, the geometric mean titers (GMTs) and the percent of subjects with VZV antibody titers ≥5 gpELISA units/mL generally increased. The GMTs and percent of subjects with VZV antibody titers ≥5 gpELISA units/mL in the 2-dose recipients were higher than those in the 1-dose recipients for the first year of follow-up and generally comparable thereafter. The cumulative rate of VZV antibody persistence with both regimens remained very high at year 9 (99.0% for the 1-dose group and 98.8% for the 2-dose group).

Two-Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who received 2 doses of vaccine, detectable VZV antibodies were present in 97.9% (568/580) at 1 year, 97.1% (34/35) at 2 years, 100% (144/144) at 3 years, 97.0% (98/101) at 4 years, 97.4% (76/78) at 5 years, and 100% (34/34) at 6 years postvaccination.

A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella, which could account for the apparent long-term persistence of antibody levels in these studies.

14.4 Studies with Other Vaccines

Concomitant Administration with M-M-R II

In combined clinical studies involving 1080 children 12 to 36 months of age, 653 received VARIVAX and M-M-R II concomitantly at separate injection sites and 427 received the vaccines six weeks apart. Seroconversion rates and antibody levels to measles, mumps, rubella, and varicella were comparable between the two groups at approximately six weeks post-vaccination.

Concomitant Administration with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Oral Poliovirus Vaccine (OPV)

In a clinical study involving 318 children 12 months to 42 months of age, 160 received an investigational varicella-containing vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with booster doses of DTaP and OPV (no longer licensed in the United States). The comparator group of 144 children received M-M-R II concomitantly with booster doses of DTaP and OPV followed by VARIVAX six weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV and the percentage of vaccinees whose titers were boosted for diphtheria, tetanus, pertussis, and polio were comparable between the two groups. Anti-VZV levels were decreased when the investigational vaccine containing varicella was administered concomitantly with DTaP {17}. No clinically significant differences were noted in adverse reactions between the two groups.

Concomitant Administration with PedvaxHIB®

In a clinical study involving 307 children 12 to 18 months of age, 150 received an investigational varicella-containing vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with a booster dose of PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], while 130 received M-M-R II concomitantly with a booster dose of PedvaxHIB followed by VARIVAX 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV, and GMTs for PedvaxHIB were comparable between the two groups. Anti-VZV levels were decreased when the investigational vaccine containing varicella was administered

concomitantly with PedvaxHIB {18}. No clinically significant differences in adverse reactions were seen between the two groups.

Concomitant Administration with M-M-R II and COMVAX

In a clinical study involving 822 children 12 to 15 months of age, 410 received COMVAX, M-M-R II, and VARIVAX concomitantly at separate injection sites, and 412 received COMVAX followed by M-M-R II and VARIVAX given concomitantly at separate injection sites, 6 weeks later. At 6 weeks postvaccination, the immune responses for the subjects who received the concomitant doses of COMVAX, M-M-R II, and VARIVAX were similar to those of the subjects who received COMVAX followed 6 weeks later by M-M-R II and VARIVAX with respect to all antigens administered. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus six weeks apart.

15 REFERENCES

1. CDC: General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 55(No. RR-15): 1-47, 2006.
2. Weibel, R.E.; et al.: Live Attenuated Varicella Virus Vaccine. Efficacy Trial in Healthy Children. N Engl J Med. 310(22): 1409-1415, 1984.
3. Arbeter, A.M.; et al.: Varicella Vaccine Trials in Healthy Children. A Summary of Comparative and Follow-up Studies. Am J Dis Child. 138: 434-438, 1984.
4. Weibel, R.E.; et al.: Live Oka/Merck Varicella Vaccine in Healthy Children. Further Clinical and Laboratory Assessment. JAMA. 254(17): 2435-2439, 1985.
5. Chartrand, D.M.; et al.: New Varicella Vaccine Production Lots in Healthy Children and Adolescents. Abstracts of the 1988 Inter-Science Conference Antimicrobial Agents and Chemotherapy: 237(Abstract #731).
6. Johnson, C.E.; et al.: Live Attenuated Varicella Vaccine in Healthy 12- to 24-Month-Old Children. Pediatrics. 81(4): 512-518, 1988.
7. Gershon, A.A.; et al.: Immunization of Healthy Adults with Live Attenuated Varicella Vaccine. J Infect Dis. 158(1): 132-137, 1988.
8. Gershon, A.A.; et al.: Live Attenuated Varicella Vaccine: Protection in Healthy Adults Compared with Leukemic Children. J Infect Dis. 161: 661-666, 1990.
9. White, C.J.; et al.: Varicella Vaccine (VARIVAX) in Healthy Children and Adolescents: Results From Clinical Trials, 1987 to 1989. Pediatrics. 87(5): 604-610, 1991.
10. Galea, S.; et al.: The Safety Profile of Varicella Vaccine: A 10-Year Review. J Infect Dis. 197(S2): 165-169, 2008.
11. Hammerschlag, M.R.; et al.: Herpes Zoster in an Adult Recipient of Live Attenuated Varicella Vaccine. J Infect Dis. 160(3): 535-537, 1989.
12. Guess, H.A.; et al.: Population-Based Studies of Varicella Complications. Pediatrics. 78(suppl): 723-727, 1986.
13. Kuter, B.J.; et al.: Ten Year Follow-up of Healthy Children who Received One or Two Injections of Varicella Vaccine. Pediatr Infect Dis J. 23: 132-37, 2004.
14. Kuter, B.J.; et al.: Oka/Merck Varicella Vaccine in Healthy Children: Final Report of a 2-Year Efficacy Study and 7-Year Follow-up Studies. Vaccine. 9: 643-647, 1991.
15. Bernstein, H.H.; et al.: Clinical Survey of Natural Varicella Compared with Breakthrough Varicella After Immunization with Live Attenuated Oka/Merck Varicella Vaccine. Pediatrics. 92(6): 833-837, 1993.

16. Wharton, M.: The Epidemiology of Varicella-zoster Virus Infections. Infect Dis Clin North Am. 10(3):571-581, 1996.

17. White, C.J. et al.: Measles, Mumps, Rubella, and Varicella Combination Vaccine: Safety and Immunogenicity Alone and in Combination with Other Vaccines Given to Children. Clin Infect Dis. 24(5): 925-931, 1997.

18. Reuman, P.D.; et al.: Safety and Immunogenicity of Concurrent Administration of Measles-Mumps-Rubella-Varicella Vaccine and PedvaxHIB® Vaccines in Healthy Children Twelve to Eighteen Months Old. Pediatr Infect Dis J. 16(7): 662-667, 1997.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4826/4309 —VARIVAX is supplied as follows:
(1) a single-dose vial of lyophilized vaccine (package A), NDC 0006-4826-00
(2) a box of 10 vials of diluent (package B).
No. 4827/4309 —VARIVAX is supplied as follows:
(1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4827-00
(2) a box of 10 vials of diluent (package B).

Storage

Vaccine Vial

During shipment, maintain the vaccine at a temperature between −58°F and +5°F (−50°C and −15°C). Use of dry ice may subject VARIVAX to temperatures colder than −58°F (−50°C).

Before reconstitution, store the lyophilized vaccine in a freezer at a temperature between −58°F and +5°F (−50°C and −15°C). Any freezer (*e.g.*, chest, frost-free) that reliably maintains a temperature between −58°F and +5°F (−50°C and −15°C) and has a separate sealed freezer door is acceptable for storing VARIVAX.VARIVAX may be stored at refrigerator temperature (36°F to 46°F, 2°C to 8°C) for up to 72 continuous hours prior to reconstitution. Vaccine stored at 2°C to 8°C which is not used within 72 hours of removal from +5°F (−15°C) storage should be discarded.

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

Diluent Vial

The vial of diluent should be stored separately at room temperature (68°F to 77°F, 20°C to 25°C), or in the refrigerator.

For further product information, call 1-800-9-VARIVAX (1-800-982-7482).

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Discuss the following with the patient:

- Question the patient, parent, or guardian about reactions to previous vaccines.
- Provide a copy of the patient information (PPI) located at the end of this insert and discuss any questions or concerns.
- Inform patient, parent, or guardian that vaccination with VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults.
- Inform female patients to avoid pregnancy for three months following vaccination.
- Inform patient, parent, or guardian of the benefits and risks of VARIVAX.
- Instruct patient, parent, or guardian to report any adverse reactions or any symptoms of concern to their healthcare professional.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at http://www.vaers.hhs.gov.

Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-v210-i-fro-1407r710

M-M-R® II
(MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

DESCRIPTION

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for vaccination against measles (rubeola), mumps, and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) ATTENUVAX® (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX® (Mumps Virus Vaccine Live), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX® II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.{1,2}

The growth medium for measles and mumps is Medium 199 (a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum) containing SPGA (sucrose, phosphate, glutamate, and recombinant human albumin) as stabilizer and neomycin.

The growth medium for rubella is Minimum Essential Medium (MEM) [a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum] containing recombinant human albumin and neomycin. Sorbitol and hydrolyzed gelatin stabilizer are added to the individual virus harvests.

The cells, virus pools, and fetal bovine serum are all screened for the absence of adventitious agents.

The reconstituted vaccine is for subcutaneous administration. Each 0.5 mL dose contains not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus; 12,500 $TCID_{50}$ of mumps virus; and 1,000 $TCID_{50}$ of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.

CLINICAL PHARMACOLOGY

Measles, mumps, and rubella are three common childhood diseases, caused by measles virus, mumps virus (paramyxoviruses), and rubella virus (togavirus), respectively, that may be associated with serious complications and/or death. For example, pneumonia and encephalitis are caused by measles. Mumps is associated with aseptic meningitis, deafness and orchitis; and rubella during pregnancy may cause congenital rubella syndrome in the infants of infected mothers.

The impact of measles, mumps, and rubella vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles, mumps, and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995. For measles, 894,134 cases reported in 1941 compared to 288 cases reported in 1995 resulted in a 99.97% decrease in reported cases; for mumps, 152,209 cases reported in 1968 compared to 840 cases reported in 1995 resulted in a 99.45% decrease in reported cases; and for rubella, 57,686 cases reported in 1969 compared to 200 cases reported in 1995 resulted in a 99.65% decrease.{3}

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons. However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose (see also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

A study{4} of 6-month-old and 15-month-old infants born to vaccine-immunized mothers demonstrated that, following vaccination with ATTENUVAX, 74% of the 6-month-old infants developed detectable neutralizing antibody (NT) titers while 100% of the 15-month-old infants developed NT. This rate of seroconversion is higher than that previously reported for 6-month-old infants born to naturally immune mothers tested by HI assay. When the 6-month-old infants of immunized mothers were revaccinated at

15 months, they developed antibody titers equivalent to the 15-month-old vaccinees. The lower seroconversion rate in 6-month-olds has two possible explanations: 1) Due to the limit of the detection level of the assays (NT and enzyme immunoassay [EIA]), the presence of trace amounts of undetectable maternal antibody might interfere with the seroconversion of infants; or 2) The immune system of 6-month-olds is not always capable of mounting a response to measles vaccine as measured by the two antibody assays.

There is some evidence to suggest that infants who are born to mothers who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.{5,6}

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components.{7-12} These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases.{13-15}

Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination.{16-18} See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing.

The RA 27/3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine{19-25} and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.{26,27} The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.{27-29} The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,{27,29-31} and provide greater confidence for lasting immunity.

INDICATIONS AND USAGE

Recommended Vaccination Schedule

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Individuals first vaccinated at 12 months of age or older should be revaccinated prior to elementary school entry. Revaccination is intended to seroconvert those who do not respond to the first dose. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of M-M-R II at 12 to 15 months of age and administration of the second dose of M-M-R II at 4 to 6 years of age.{32} In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.

Measles Outbreak Schedule

Infants Between 6 to 12 Months of Age

Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion (see CLINICAL PHARMACOLOGY). Such infants should receive a second dose of M-M-R II between 12 to 15 months of age followed by revaccination at elementary school entry.{32}

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Other Vaccination Considerations

Non-Pregnant Adolescent and Adult Females

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.{33}

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reasons for this precaution.

The ACIP has stated "If it is practical and if reliable laboratory services are available, women of childbearing age who are potential candidates for vaccination can have serologic tests to determine susceptibility to rubella. However, with the exception of premarital and prenatal screening, routinely performing serologic tests for all women of childbearing age to determine susceptibility (so that vaccine is given only to proven susceptible women) can be effective but is expensive. Also, 2 visits to the health-care provider would be necessary — one for screening and one for vaccination. Accordingly, rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing — and may be preferable, particularly when costs of serology are high and follow-up of identified susceptible women for vaccination is not assured."{33}

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

Postpartum Women

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (see PRECAUTIONS, *Nursing Mothers*).

Other Populations

Previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women should receive live attenuated rubella vaccine (such as that contained in monovalent rubella vaccine or in M-M-R II) to reduce the risk of exposure of the pregnant woman.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps, or rubella and import these diseases into the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can either receive the indicated monovalent vaccine (measles, mumps, or rubella), or a combination vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if monovalent measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.{34-36}

Vaccination is recommended for susceptible individuals in high-risk groups such as college students, health-care workers, and military personnel.{33,34,37}

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.{34}

The ACIP recommends that "Persons vaccinated with inactivated vaccine followed within 3 months by live vaccine should be revaccinated with two doses of live vaccine. Revaccination is particularly important when the risk of exposure to wild-type measles virus is increased, as may occur during international travel."{34}

Post-Exposure Vaccination

Vaccination of individuals exposed to wild-type measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a few days before exposure, substantial protection may be afforded.{34,38,39} There is no conclusive evidence that vaccination of individuals recently exposed to wild-type mumps or wild-type rubella will provide protection.{33,37}

Use With Other Vaccines

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including gelatin.{40}

Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and PRECAUTIONS, *Pregnancy*).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Febrile respiratory illness or other active febrile infection. However, the ACIP has recommended that all vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper respiratory infection with or without low-grade fever, or other low-grade febrile illness.{41}

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;{41-43} cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis{44} (MIBE), pneumonitis{45} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

WARNINGS

Due caution should be employed in administration of M-M-R II to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).{46}

However, the AAP has stated, "Most children with a history of anaphylactic reactions to eggs have no untoward reactions to measles or MMR vaccine. Persons are not at increased risk if they have egg allergies that are not anaphylactic, and they should be vaccinated in the usual manner. In addition, skin testing of egg-allergic children with vaccine has not been predictive of which children will have an immediate hypersensitivity reaction...Persons with allergies to chickens or chicken feathers are not at increased risk of reaction to the vaccine."{47}

Hypersensitivity to Neomycin

The AAP states, "Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive measles vaccine. Most often, however, neomycin allergy manifests as a contact dermatitis, which is a delayed-type (cell-mediated) immune response rather than anaphylaxis. In such persons, an adverse reaction to neomycin in the vaccine would be an erythematous, pruritic nodule or papule, 48 to 96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine."{47}

Thrombocytopenia

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases (see ADVERSE REACTIONS).

PRECAUTIONS

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Special care should be taken to ensure that the injection does not enter a blood vessel.

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see CONTRAINDICATIONS).{42,43}

Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immune globulin (human).{47}

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.{33} However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R II.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine;{48} no studies have been reported to date of the effect of measles virus vaccines on untreated tuberculous children. However, individuals with active untreated tuberculosis should not be vaccinated.

As for any vaccine, vaccination with M-M-R II may not result in protection in 100% of vaccinees.

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of M-M-R II or other measles-, mumps-, or rubella-containing vaccines.

Information for Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.{49}

Pregnancy should be avoided for 3 months following vaccination, and patients should be informed of the reasons for this precaution (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, CONTRAINDICATIONS, and PRECAUTIONS, *Pregnancy*).

Laboratory Tests

See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY.

Drug Interactions

See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.

Immunosuppressive Therapy

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g. nasal, skin), long-term alternate-day

treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of [measles, mumps, or rubella vaccine]."{33,34,37}

Immune Globulin

Administration of immune globulins concurrently with M-M-R II may interfere with the expected immune response.{33,34,47}

See also PRECAUTIONS, *General*.

Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with M-M-R II. It is also not known whether M-M-R II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome;{50} (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans;{37} and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to infection with wild-type measles during pregnancy.{51,52} There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

Nursing Mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants.{53} In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.{54,55} Caution should be exercised when M-M-R II is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established (see also CLINICAL PHARMACOLOGY). Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of monovalent or bivalent vaccine containing measles, mumps, or rubella:

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. This type of involvement as well as myalgia and paresthesia, have also been reported following administration of MERUVAX II.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0-3%; women: 12-26%),{17,56,57} and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in women older than 35 years, these reactions are generally well tolerated and rarely interfere with normal activities.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS); subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines.

The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases).{58,59}

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported (see CONTRAINDICATIONS). In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.{60}

Cases of aseptic meningitis have been reported to VAERS following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Respiratory System

Pneumonia; pneumonitis (see CONTRAINDICATIONS); sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; erythema multiforme; urticaria; rash; measles-like rash; pruritis.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; induration; tenderness; vesiculation at injection site.

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see CONTRAINDICATIONS). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.{61}

Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events.{49} A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravascularly.

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*.

Children first vaccinated when younger than 12 months of age should receive another dose between 12 to 15 months of age followed by revaccination prior to elementary school entry.{32} See also INDICATIONS AND USAGE, *Measles Outbreak Schedule*.

Immune Globulin (IG) is not to be given concurrently with M-M-R II (see PRECAUTIONS, *General* and PRECAUTIONS, *Drug Interactions*).

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. M-M-R II, when reconstituted, is clear yellow.

Use With Other Vaccines

M-M-R II should be given one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB® [*Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate injection sites and syringes. No impairment of immune response to individually tested

vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTaP [or DTwP], IPV [or OPV], Hib with or without Hepatitis B vaccine, and varicella vaccine), data from numerous studies have indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended."{62}

HOW SUPPLIED

No. 4681 — M-M-R II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4681-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.

Storage

To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).

Protect the vaccine from light at all times, since such exposure may inactivate the viruses.

Before reconstitution, store the lyophilized vaccine at 36°F to 46°F (2°C to 8°C). The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. **Do not freeze the diluent.**

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 36°F to 46°F (2°C to 8°C) and discard if not used within 8 hours.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

REFERENCES

1. Plotkin, S.A.; Cornfeld, D.; Ingalls, T.H.: Studies of Immunization with living rubella virus: Trials in children with a strain cultured from an aborted fetus, Am. J. Dis. Child. *110:* 381-389, 1965.
2. Plotkin, S.A.; Farquhar, J.; Katz, M.; Ingalls, T.H.: A new attenuated rubella virus grown in human fibroblasts: Evidence for reduced nasopharyngeal excretion, Am. J. Epidemiol. *86:* 468-477, 1967.
3. Monthly Immunization Table, MMWR *45*(1): 24-25, January 12, 1996.
4. Johnson, C.E.; et al: Measles Vaccine Immunogenicity in 6- Versus 15-Month-Old Infants Born to Mothers in the Measles Vaccine Era, Pediatrics, *93*(6): 939-943, 1994.
5. Linneman, C.C.; et al: Measles Immunity After Vaccination: Results in Children Vaccinated Before 10 Months of Age, Pediatrics, *69*(3): 332-335, March 1982.
6. Stetler, H.C.; et al: Impact of Revaccinating Children Who Initially Received Measles Vaccine Before 10 Months of Age, Pediatrics *77*(4): 471-476, April 1986.
7. Hilleman, M.R.; Buynak, E.B.; Weibel, R.E.; et al: Development and Evaluation of the Moraten Measles Virus Vaccine, JAMA *206*(3): 587-590, 1968.
8. Weibel, R.E.; Stokes, J.; Buynak, E.B.; et al: Live, Attenuated Mumps Virus Vaccine 3. Clinical and Serologic Aspects in a Field Evaluation, N. Engl. J. Med. *276:* 245-251, 1967.
9. Hilleman, M.R.; Weibel, R.E.; Buynak, E.B.; et al: Live, Attenuated Mumps Virus Vaccine 4. Protective Efficacy as Measured in a Field Evaluation, N. Engl. J. Med. *276:* 252-258, 1967.
10. Cutts, F.T.; Henderson, R.H.; Clements, C.J.; et al: Principles of measles control, Bull WHO *69*(1): 1-7, 1991.
11. Weibel, R.E.; Buynak, E.B.; Stokes, J.; et al: Evaluation Of Live Attenuated Mumps Virus Vaccine, Strain Jeryl Lynn, First International Conference on Vaccines Against Viral and Rickettsial Diseases of Man, World Health Organization, No. 147, May 1967.
12. Leibhaber, H.; Ingalls, T.H.; LeBouvier, G.L.; et al: Vaccination With RA 27/3 Rubella Vaccine, Am. J. Dis. Child. *123:* 133-136, February 1972.
13. Rosen, L.: Hemagglutination and Hemagglutination-Inhibition with Measles Virus, Virology *13:* 139-141, January 1961.

14. Brown, G.C.; et al: Fluorescent-Antibody Marker for Vaccine-Induced Rubella Antibodies, Infection and Immunity 2(4): 360-363, 1970.

15. Buynak, E.B.; et al: Live Attenuated Mumps Virus Vaccine 1. Vaccine Development, Proceedings of the Society for Experimental Biology and Medicine, *123:* 768-775, 1966.

16. Weibel, R.E.; Carlson, A.J.; Villarejos, V.M.; Buynak, E.B.; McLean, A.A.; Hilleman, M.R.: Clinical and Laboratory Studies of Combined Live Measles, Mumps, and Rubella Vaccines Using the RA 27/3 Rubella Virus, Proc. Soc. Exp. Biol. Med. *165:* 323-326, 1980.

17. Unpublished data from the files of Merck Research Laboratories.

18. Watson, J.C.; Pearson, J.S.; Erdman, D.D.; et al: An Evaluation of Measles Revaccination Among School-Entry Age Children, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract #268, 143, 1991.

19. Fogel, A.; Moshkowitz, A.; Rannon, L.; Gerichter, Ch.B.: Comparative trials of RA 27/3 and Cendehill rubella vaccines in adult and adolescent females, Am. J. Epidemiol. *93:* 392-393, 1971.

20. Andzhaparidze, O.G.; Desyatskova, R.G.; Chervonski, G.I.; Pryanichnikova, L.V.: Immunogenicity and reactogenicity of live attenuated rubella virus vaccines, Am. J. Epidemiol. *91:* 527-530, 1970.

21. Freestone, D.S.; Reynolds, G.M.; McKinnon, J.A.; Prydie, J.: Vaccination of schoolgirls against rubella. Assessment of serological status and a comparative trial of Wistar RA 27/3 and Cendehill strain live attenuated rubella vaccines in 13-year-old schoolgirls in Dudley, Br. J. Prev. Soc. Med. *29:* 258-261, 1975.

22. Grillner, L.; Hedstrom, C.E.; Bergstrom, H.; Forssman, L.; Rigner, A.; Lycke, E.: Vaccination against rubella of newly delivered women, Scand. J. Infect. Dis. *5:* 237-241, 1973.

23. Grillner, L.: Neutralizing antibodies after rubella vaccination of newly delivered women: a comparison between three vaccines, Scand. J. Infect. Dis. *7:* 169-172, 1975.

24. Wallace, R.B.; Isacson, P.: Comparative trial of HPV-77, DE-5 and RA 27/3 live-attenuated rubella vaccines, Am. J. Dis. Child. *124:* 536-538, 1972.

25. Lalla, M.; Vesikari, T.; Virolainen, M.: Lymphoblast proliferation and humoral antibody response after rubella vaccination, Clin. Exp. Immunol. *15:* 193-202, 1973.

26. LeBouvier, G.L.; Plotkin, S.A.: Precipitin responses to rubella vaccine RA 27/3, J. Infect. Dis. *123:* 220-223, 1971.

27. Horstmann, D.M.: Rubella: The challenge of its control, J. Infect. Dis. *123:* 640-654, 1971.

28. Ogra, P.L.; Kerr-Grant, D.; Umana, G.; Dzierba, J.; Weintraub, D.: Antibody response in serum and nasopharynx after naturally acquired and vaccine-induced infection with rubella virus, N. Engl. J. Med. *285:* 1333-1339, 1971.

29. Plotkin, S.A.; Farquhar, J.D.; Ogra, P.L.: Immunologic properties of RA 27/3 rubella virus vaccine, J. Am. Med. Assoc. *225:* 585-590, 1973.

30. Liebhaber, H.; Ingalls, T.H.; LeBouvier, G.L.; Horstmann, D.M.: Vaccination with RA 27/3 rubella vaccine. Persistence of immunity and resistance to challenge after two years, Am. J. Dis. Child. *123:* 133-136, 1972.

31. Farquhar, J.D.: Follow-up on rubella vaccinations and experience with subclinical reinfection, J. Pediatr. *81:* 460-465, 1972.

32. Measles, Mumps, and Rubella — Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR *47*(RR-8): May 22, 1998.

33. Rubella Prevention: Recommendation of the Immunization Practices Advisory Committee (ACIP), MMWR *39*(RR-15): 1-18, November 23, 1990.

34. Measles Prevention: Recommendations of the Immunization Practices Advisory Committee (ACIP), MMWR *38*(S-9): 5-22, December 29, 1989.

35. Jong, E.C., The Travel and Tropical Medicine Manual, W.B. Saunders Company, p. 12-16, 1987.

36. Committee on Immunization Council of Medical Societies, American College of Physicians, Phila., PA, Guide for Adult Immunization, First Edition, 1985.

37. Recommendations of the Immunization Practices Advisory Committee (ACIP), Mumps Prevention, MMWR *38*(22): 388-400, June 9, 1989.

38. King, G.E.; Markowitz, L.E.; Patriarca, P.A.; et al: Clinical Efficacy of Measles Vaccine During the 1990 Measles Epidemic, Pediatr. Infect. Dis. J. *10*(12): 883-888, December 1991.

39. Krasinski, K.; Borkowsky, W.: Measles and Measles Immunity in Children Infected With Human Immunodeficiency Virus, JAMA *261*(17): 2512-2516, 1989.

40. Kelso, J.M.; Jones, R.T.; Yunginger, J.W.: Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin, J. Allergy Clin. Immunol. *91:* 867-872, 1993.

41. General Recommendations on Immunization, Recommendations of the Advisory Committee on Immunization Practices, MMWR *43*(RR-1): 1-38, January 28, 1994.

42. Center for Disease Control: Immunization of Children Infected with Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus, Annals of Internal Medicine, *106*: 75-78, 1987.

43. Krasinski, K.; Borkowsky, W.; Krugman, S.: Antibody following measles immunization in children infected with human T-cell lymphotropic virus-type III/lymphadenopathy associated virus (HTLV-III/LAV) [Abstract]. In: Program and abstracts of the International Conference on Acquired Immunodeficiency Syndrome, Paris, France, June 23-25, 1986.

44. Bitnum, A.; et al: Measles Inclusion Body Encephalitis Caused by the Vaccine Strain of Measles Virus. Clin. Infect. Dis. *29*: 855-861, 1999.

45. Angel, J.B.; et al: Vaccine Associated Measles Pneumonitis in an Adult with AIDS. Annals of Internal Medicine, *129*: 104-106, 1998.

46. Isaacs, D.; Menser, M.: Modern Vaccines, Measles, Mumps, Rubella, and Varicella, Lancet *335*: 1384-1387, June 9, 1990.

47. Peter, G.; et al (eds): Report of the Committee on Infectious Diseases, Twenty-fourth Edition, American Academy of Pediatrics, 344-357, 1997.

48. Starr, S.; Berkovich, S.: The effect of measles, gamma globulin modified measles, and attenuated measles vaccine on the course of treated tuberculosis in children, Pediatrics *35*: 97-102, January 1965.

49. Vaccine Adverse Event Reporting System — United States, MMWR *39*(41): 730-733, October 19, 1990.

50. Rubella vaccination during pregnancy — United States, 1971-1981. MMWR *31*(35): 477-481, September 10, 1982.

51. Eberhart-Phillips, J.E.; et al: Measles in pregnancy: a descriptive study of 58 cases. Obstetrics and Gynecology, *82*(5): 797-801, November 1993.

52. Jespersen, C.S.; et al: Measles as a cause of fetal defects: A retrospective study of ten measles epidemics in Greenland. Acta Paediatr Scand. *66*: 367-372, May 1977.

53. Losonsky, G.A.; Fishaut, J.M.; Strussenber, J.; Ogra, P.L.: Effect of immunization against rubella on lactation products. II. Maternal-neonatal interactions, J. Infect. Dis. *145*: 661-666, 1982.

54. Landes, R.D.; Bass, J.W.; Millunchick, E.W.; Oetgen, W.J.: Neonatal rubella following postpartum maternal immunization, J. Pediatr. *97*: 465-467, 1980.

55. Lerman, S.J.: Neonatal rubella following postpartum maternal immunization, J. Pediatr. *98*: 668, 1981. (Letter)

56. Gershon, A.; et al: Live attenuated rubella virus vaccine: comparison of responses to HPV-77-DE5 and RA 27/3 strains, Am. J. Med. Sci. *279*(2): 95-97, 1980.

57. Weibel, R.E.; et al: Clinical and laboratory studies of live attenuated RA 27/3 and HPV-77-DE rubella virus vaccines, Proc. Soc. Exp. Biol. Med. *165*: 44-49, 1980.

58. Bennetto, L; Scolding, N. Inflammatory/post-infectious encephalomyelitis. J Neurol Neurosurg Psychiatry 2004;75(Suppl 1):i22-8.

59. Fenichel, GM. Neurological complications of immunization. AnnNeurol 1982;12(2):119-28.

60. CDC, Measles Surveillance, Report No. 11, p. 14, September 1982.

61. Peltola, H.; et al: The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two dose vaccination program. N. Engl. J. Med. *331*: 1397-1402, 1994.

62. Centers for Disease Control and Prevention. Recommended childhood immunization schedule — United States, January-June 1996, MMWR *44*(51 & 52): 940-943, January 5, 1996.

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MORAL REFLECTIONS ON VACCINES PREPARED FROM CELLS DERIVED FROM ABORTED HUMAN FOETUSES

The matter in question regards the lawfulness of production, distribution and use of certain vaccines whose production is connected with acts of procured abortion. It concerns vaccines containing live viruses which have been prepared from human cell lines of foetal origin, using tissues from aborted human foetuses as a source of such cells. The best known, and perhaps the most important due to its vast distribution and its use on an almost universal level, is the vaccine against Rubella (German measles).

Rubella and its vaccine

Rubella (German measles)[1] is a viral illness caused by a Togavirus of the genus *Rubivirus* and is characterized by a maculopapular rash. It consists of an infection which is common in infancy and has no clinical manifestations in one case out of two, is self-limiting and usually benign. Nonetheless, the German measles virus is one of the most pathological infective agents for the embryo and foetus. When a woman catches the infection during pregnancy, especially during the first trimester, the risk of foetal infection is very high (approximately 95%). The virus replicates itself in the placenta and infects the foetus, causing the constellation of abnormalities denoted by the name of *Congenital Rubella Syndrome*. For example, the severe epidemic of German measles which affected a huge part of the United States in 1964 thus caused 20,000 cases of congenital rubella[2], resulting in 11,250 abortions (spontaneous or surgical), 2,100 neonatal deaths, 11,600 cases of deafness, 3,580 cases of blindness, 1,800 cases of mental retardation. It was this epidemic that pushed for the development and introduction on the market of an effective vaccine against rubella, thus permitting an effective prophylaxis against this infection.

The severity of congenital rubella and the handicaps which it causes justify systematic vaccination against such a sickness. It is very difficult, perhaps even impossible, to avoid the infection of a pregnant woman, even if the rubella infection of a person in contact with this woman is diagnosed from the first day of the eruption of the rash. Therefore, one tries to prevent transmission by suppressing the reservoir of infection among children who have not been vaccinated, by means of early immunization of all children (universal vaccination). Universal vaccination has resulted in a considerable fall in the incidence of congenital rubella, with a general incidence reduced to less than 5 cases per 100,000 livebirths. Nevertheless, this progress remains fragile. In the United States, for example, after an overwhelming reduction in the number of cases of congenital rubella to only a few cases annually,

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[1] J. E. Banatvala, D.W.G. Brown, *Rubella*, The Lancet, 3rd April 2004, vol. 363, No. 9415, pp.1127-1137

[2] *Rubella* , Morbidity and Mortality Weekly Report, 1964, vol. 13, p.93. S.A. Plotkin, *Virologic Assistance in the Management of German Measles in Pregnancy*, JAMA, 26th October 1964, vol.190, pp.265-268

i.e. less than 0.1 per 100,000 live births, a new epidemic wave came on in 1991, with an incidence that rose to 0.8/100,000. Such waves of resurgence of German measles were also seen in 1997 and in the year 2000. These periodic episodes of resurgence make it evident that there is a persistent circulation of the virus among young adults, which is the consequence of insufficient vaccination coverage. The latter situation allows a significant proportion of vulnerable subjects to persist, who are a source of periodic epidemics which put women in the fertile age group who have not been immunized at risk. Therefore, the reduction to the point of eliminating congenital rubella is considered a priority in public health care.

Vaccines currently produced using human cell lines that come from aborted foetuses

To date, there are two human diploid cell lines which were originally prepared from tissues of aborted foetuses (in 1964 and 1970) and are used for the preparation of vaccines based on live attenuated virus: the first one is the WI-38 line (Winstar Institute 38), with human diploid lung fibroblasts, coming from a female foetus that was aborted because the family felt they had too many children (G. Sven *et al.*, 1969). It was prepared and developed by Leonard Hayflick in 1964 (L. Hayflick, 1965; G. Sven *et al.*, 1969)[3] and bears the ATCC number CCL-75. WI-38 has been used for the preparation of the historical vaccine RA 27/3 against rubella (S.A. Plotkin *et al*, 1965)[4]. The second human cell line is MRC-5 (Medical Research Council 5) (human, lung, embryonic) (ATCC number CCL-171), with human lung fibroblasts coming from a 14 week male foetus aborted for "psychiatric reasons" from a 27 year old woman in the UK. MRC-5 was prepared and developed by J.P. Jacobs in 1966 (J.P. Jacobs *et al,* 1970)[5]. Other human cell lines have been developed for pharmaceutical needs, but are not involved in the vaccines actually available[6].

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[3]. L. Hayflick, *The Limited* In Vitro *Lifetime of Human Diploid Cell Strains*, Experimental Cell Research, March 1965, vol.37, no. 3, pp. 614-636.
G. Sven, S. Plotkin, K. McCarthy, *Gamma Globulin Prophylaxis; Inactivated Rubella Virus; Production and Biological Control of Live Attenuated Rubella Virus Vaccines*, American journal of Diseases of Children, August 1969, vol. 118, no. 2, pp.372-381.

[4].S. A. Plotkin, D. Cornfeld, Th.H. Ingalls, *Studies of Immunization With Living Rubella Virus, Trials in Children With a Strain coming from an Aborted Fetus*, American Journal of Diseases in children, October 1965, vol. 110, no. 4, pp.381-389.

[5] .J.P. Jacobs, C.M. Jones, J.P. Baille, Characteristics of a Human Diploid Cell Designated MRC-5, Nature, 11th July 1970, vol.277, pp.168-170.

[6] Two other human cell lines, that are permanent, HEK 293 aborted fetal cell line, from primary human embryonic kidney cells transformed by sheared adenovirus type 5 (the fetal kidney material was obtained from an aborted fetus, in 1972 probably), and PER.C6, a fetal cell line created using retinal tissue from an 18 week gestation aborted baby, have been developed for the pharmaceutical manufacturing of adenovirus vectors (for gene therapy). They have not been involved in the making of any of the attenuated live viruses vaccines presently in use because of their capacity to develop tumorigenic cells in the recipient. However some vaccines, still at the developmental stage, against Ebola virus (Crucell,NV and the Vaccine Research Center of the National Institutes of Health's Allergy and Infectious Diseases, NIAID), HIV (Merck), influenza (MedImmune, Sanofi pasteur), Japanese encephalitis (Crucell N.V. and Rhein Biotech N.V.) are prepared using PER.C6® cell line (Crucell N.V., Leiden, The Netherlands).

The vaccines that are incriminated today as using human cell lines from aborted foetuses, WI-38 and MRC-5, are the following: [7]

A) Live vaccines against rubella[8]*:*
- the monovalent vaccines against rubella Meruvax®II (Merck) (U.S.), Rudivax® (Sanofi Pasteur, Fr.), and Ervevax® (RA 27/3) (GlaxoSmithKline, Belgium);
- the combined vaccine MR against rubella and measles, commercialized with the name of M-R-VAX® (Merck, US) and Rudi-Rouvax® (AVP, France);
- the combined vaccine against rubella and mumps marketed under the name of Biavax®II (Merck, U.S.),
- the combined vaccine MMR (*measles, mumps, rubella*) against rubella, mumps and measles, marketed under the name of M-M-R® II (Merck, US), R.O.R.®, Trimovax® (Sanofi Pasteur, Fr.), and Priorix® (GlaxoSmithKline UK).

B) Other vaccines, also prepared using human cell lines from aborted foetuses:
- two vaccines against hepatitis A, one produced by Merck (VAQTA), the other one produced by GlaxoSmithKline (HAVRIX), both of them being prepared using MRC-5;
- one vaccine against chicken pox, Varivax®, produced by Merck using WI-38 and MRC-5;
- one vaccine against poliomyelitis, the inactivated polio virus vaccine Poliovax® (Aventis-Pasteur, Fr.) using MRC-5;
- one vaccine against rabies, Imovax®, produced by Aventis Pasteur, harvested from infected human diploid cells, MRC-5 strain;
- one vaccine against smallpox, ACAM 1000, prepared by Acambis using MRC-5, still on trial.

<u>The position of the ethical problem related to these vaccines</u>

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[7] Against these various infectious diseases, there are some alternative vaccines that are prepared using animals' cells or tissues, and are therefore ethically acceptable. Their availability depends on the country in question. Concerning the particular case of the United States, there are no options for the time being in that country for the vaccination against rubella, chickenpox and hepatitis A, other than the vaccines proposed by Merck, prepared using the human cell lines WI-38 and MRC-5. There is a vaccine against smallpox prepared with the Vero cell line (derived from the kidney of an African green monkey), ACAM2000 (Acambis-Baxter) (a second-generation smallpox vaccine, stockpiled, not approved in the US), which offers, therefore, an alternative to the Acambis 1000. There are alternative vaccines against mumps (Mumpsvax, Merck, measles (Attenuvax, Merck), rabies (RabAvert, Chiron therapeutics), prepared from chicken embryos. (However serious allergies have occurred with such vaccines), poliomyelitis (IPOL, Aventis-Pasteur, prepared with monkey kidney cells) and smallpox (a third-generation smallpox vaccine MVA, Modified Vaccinia Ankara, Acambis-Baxter).

In Europe and in Japan, there are other vaccines available against rubella and hepatitis A, produced using non-human cell lines. The Kitasato Institute produce four vaccines against rubella, called Takahashi, TO-336 and Matuba, prepared with cells from rabbit kidney, and one (Matuura) prepared with cells from a quail embryo. The Chemo-sero-therapeutic Research Institute Kaketsuken produce one another vaccine against hepatitis A, called Ainmugen, prepared with cells from monkey kidney. The only remaining problem is with the vaccine Varivax® against chicken pox, for which there is no alternative.

[8] The vaccine against rubella using the strain Wistar RA27/3 of live attenuated rubella virus, adapted and propagated in WI-38 human diploid lung fibroblasts is at the centre of present controversy regarding the morality of the use of vaccines prepared with the help of human cell lines coming from aborted foetuses.

From the point of view of prevention of viral diseases such as German measles, mumps, measles, chicken pox and hepatitis A, it is clear that the making of effective vaccines against diseases such as these, as well as their use in the fight against these infections, up to the point of eradication, by means of an obligatory vaccination of all the population at risk, undoubtedly represents a "milestone" in the secular fight of man against infective and contagious diseases.

However, as the same vaccines are prepared from viruses taken from the tissues of foetuses that had been infected and voluntarily aborted, and the viruses were subsequently attenuated and cultivated from human cell lines which come likewise from procured abortions, they do not cease to pose ethical problems. The need to articulate a moral reflection on the matter in question arises mainly from the connection which exists between the vaccines mentioned above and the procured abortions from which biological material necessary for their preparation was obtained.

If someone rejects every form of voluntary abortion of human foetuses, would such a person not contradict himself/herself by allowing the use of these vaccines of live attenuated viruses on their children? Would it not be a matter of true (and illicit) cooperation in evil, even though this evil was carried out forty years ago?

Before proceeding to consider this specific case, we need to recall briefly the principles assumed in classical moral doctrine with regard to the problem of *cooperation in evil*[9], a problem which arises every time that a moral agent perceives the existence of a link between his own acts and a morally evil action carried out by others.

The principle of *licit cooperation in evil*

The first fundamental distinction to be made is that between *formal* and *material cooperation*. *Formal cooperation* is carried out when the moral agent cooperates with the immoral action of another person, sharing in the latter's evil intention. On the other hand, when a moral agent cooperates with the immoral action of another person, without sharing his/her evil intention, it is a case of *material cooperation*.

Material cooperation can be further divided into categories of *immediate* (direct) and *mediate* (indirect), depending on whether the cooperation is in the execution of the sinful action *per se*, or whether the agent acts by fulfilling the conditions – either by providing instruments or products – which make it possible to commit the immoral act. Furthermore, forms of *proximate cooperation* and *remote cooperation* can be distinguished, in relation to the "distance" (be it in terms of *temporal* space or *material* connection) between the act of cooperation and the sinful act committed by someone else. *Immediate material cooperation* is always *proximate*, while *mediate material cooperation* can be either *proximate* or *remote*.

Formal cooperation is always morally illicit because it represents a form of direct and intentional participation in the sinful action of another person.[10] *Material*

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[10] D.M. Prummer O. Pr., *De cooperatione ad malum*, in *Manuale Theologiae Moralis secundum Principia S. Thomae Aquinatis*, Tomus I, Friburgi Brisgoviae, Herder & Co., 1923, Pars I, Trat. IX, Caput III, no. 2, pp. 429-434.
.K.H. Peschke, *Cooperation in the sins of others*, in Christian Ethics. *Moral Theology in the Light of Vatican II*, vol.I, General Moral Theology, C. Goodliffe Neale Ltd., Arden Forest Industrial Estate, Alcester, Warwickshire, B49 6Er, revised edition, 1986, pp. 320-324.
.A. Fisher, *Cooperation in Evil*, Catholic Medical Quarterly, 1994, pp. 15-22.

cooperation can sometimes be illicit (depending on the conditions of the "double effect" or "indirect voluntary" action), but when *immediate material cooperation* concerns grave attacks on human life, it is always to be considered illicit, given the precious nature of the value in question[11].

A further distinction made in classical morality is that between *active* (or positive) cooperation in evil and *passive* (or negative) cooperation in evil, the former referring to the performance of an act of cooperation in a sinful action that is carried out by another person, while the latter refers to the omission of an act of denunciation or impediment of a sinful action carried out by another person, insomuch as there was a moral duty to do that which was omitted[12]. Passive cooperation can also be formal or material, immediate or mediate, proximate or remote. Obviously, every type of formal passive cooperation is to be considered illicit, but even passive material cooperation should generally be avoided, although it is admitted (by many authors) that there is not a rigorous obligation to avoid it in a case in which it would be greatly difficult to do so.

Application to the use of vaccines prepared from cells coming from embryos or foetuses aborted voluntarily

In the specific case under examination, there are three categories of people who are involved in the cooperation in evil, evil which is obviously represented by the action of a voluntary abortion performed by others: a) those who prepare the vaccines using human cell lines coming from voluntary abortions; b) those who participate in the mass marketing of such vaccines; c) those who need to use them for health reasons.

Firstly, one must consider morally illicit every form of *formal* cooperation (sharing the evil intention) in the action of those who have performed a voluntary abortion, which in turn has allowed the retrieval of foetal tissues, required for the preparation of vaccines. Therefore, whoever – regardless of the category to which he belongs – cooperates in some way, sharing its intention, to the performance of a voluntary abortion with the aim of producing the above-mentioned vaccines, participates, in actuality, in the same moral evil as the person who has performed that abortion. Such participation would also take place in the case where someone, sharing the intention of the abortion, refrains from denouncing or criticizing this illicit action, although having the moral duty to do so (*passive formal cooperation*).

.D. Tettamanzi, *Cooperazione*, in *Dizionario di Bioetica*, S. Leone, S. Privitera ed., Istituto Siciliano di Bioetica, EDB-ISB, 1994, pp.194-198.
.L. Melina, *La cooperazione con azioni moralmente cattive contro la vita umana*, in *Commentario Interdisciplinare alla "Evangelium Vitae"*, E. Sgreccia, Ramòn Luca Lucas ed., Libreria Editrice Vaticana, 1997, pp.467-490.
.E. Sgreccia, *Manuale di Bioetica*, vol. I, Reprint of the third edition, Vita e Pensiero, Milan, 1999, pp.362-363.

[11] Cf. John Paul II, Enc. *Evangelium Vitae*, no. 74.

[12] No. 1868 of the *Catechism of the Catholic Church*.

In a case where there is no such formal sharing of the immoral intention of the person who has performed the abortion, any form of cooperation would be *material*, with the following specifications.

As regards the preparation, distribution and marketing of vaccines produced as a result of the use of biological material whose origin is connected with cells coming from foetuses voluntarily aborted, such a process is stated, as a matter of principle, morally illicit, because it could contribute in encouraging the performance of other voluntary abortions, with the purpose of the production of such vaccines. Nevertheless, it should be recognized that, within the chain of production-distribution-marketing, the various cooperating agents can have different moral responsibilities.

However, there is another aspect to be considered, and that is the form of *passive material cooperation* which would be carried out by the producers of these vaccines, if they do not denounce and reject publicly the original immoral act (the voluntary abortion), and if they do not dedicate themselves together to research and promote alternative ways, exempt from moral evil, for the production of vaccines for the same infections. Such *passive material cooperation*, if it should occur, is equally illicit.

As regards those who need to use such vaccines for reasons of health, it must be emphasized that, apart from every form of *formal cooperation*, in general, doctors or parents who resort to the use of these vaccines for their children, in spite of knowing their origin (voluntary abortion), carry out a form of *very remote mediate material cooperation*, and thus very mild, in the performance of the original act of abortion, and a *mediate material cooperation*, with regard to the marketing of cells coming from abortions, and *immediate*, with regard to the marketing of vaccines produced with such cells. The cooperation is therefore more intense on the part of the authorities and national health systems that accept the use of the vaccines.

However, in this situation, the aspect of *passive cooperation* is that which stands out most. It is up to the faithful and citizens of upright conscience (fathers of families, doctors, etc.) to oppose, even by making an objection of conscience, the ever more widespread attacks against life and the "culture of death" which underlies them. From this point of view, the use of vaccines whose production is connected with procured abortion constitutes at least a mediate remote passive material cooperation to the abortion, and an immediate passive material cooperation with regard to their marketing. Furthermore, on a cultural level, the use of such vaccines contributes in the creation of a generalized social consensus to the operation of the pharmaceutical industries which produce them in an immoral way.

Therefore, doctors and fathers of families have a duty to take recourse to alternative vaccines[13] (if they exist), putting pressure on the political authorities and

[13] The alternative vaccines in question are those that are prepared by means of cell lines which are not of human origin, for example, the Vero cell line (from monkeys) (D. Vinnedge), the kidney cells of rabbits or monkeys, or the cells of chicken embryos. However, it should be noted that grave forms of allergy have occurred with some of the vaccines prepared in this way. The use of recombinant DNA technology could lead to the development of new vaccines in the near future which will no longer require the use of cultures of human diploid cells for the attenuation of the virus and its growth, for such vaccines will not be prepared from a basis of attenuated virus, but from the genome of the virus and from the antigens thus developed (G. C. Woodrow, W.M. McDonnell and F.K. Askari). Some experimental studies have already been done using vaccines developed from DNA that has been derived from the genome of the German measles virus. Moreover, some Asiatic researchers are trying to use the Varicella virus as a vector for the insertion of genes which codify the viral antigens of

health systems so that other vaccines without moral problems become available. They should take recourse, if necessary, to the use of conscientious objection[14] with regard to the use of vaccines produced by means of cell lines of aborted human foetal origin. Equally, they should oppose by all means (in writing, through the various associations, mass media, etc.) the vaccines which do not yet have morally acceptable alternatives, creating pressure so that alternative vaccines are prepared, which are not connected with the abortion of a human foetus, and requesting rigorous legal control of the pharmaceutical industry producers.

As regards the diseases against which there are no alternative vaccines which are available and ethically acceptable, it is right to abstain from using these vaccines if it can be done without causing children, and indirectly the population as a whole, to undergo significant risks to their health. However, if the latter are exposed to considerable dangers to their health, vaccines with moral problems pertaining to them may also be used on a temporary basis. The moral reason is that the duty to avoid *passive material cooperation* is not obligatory if there is grave inconvenience. Moreover, we find, in such a case, a *proportional reason,* in order to accept the use of these vaccines in the presence of the danger of favouring the spread of the pathological agent, due to the lack of vaccination of children. This is particularly true in the case of vaccination against German measles[15].

In any case, there remains a moral duty to continue to fight and to employ every lawful means in order to make life difficult for the pharmaceutical industries which act unscrupulously and unethically. However, the burden of this important battle cannot and must not fall on innocent children and on the health situation of the population – especially with regard to pregnant women.

To summarize, it must be confirmed that:

-there is a grave responsibility to use alternative vaccines and to make a conscientious objection with regard to those which have moral problems;
- as regards the vaccines without an alternative, the need to contest so that others may be prepared must be reaffirmed, as should be the lawfulness of using the former in the meantime insomuch as is necessary in order to avoid a serious risk not only for one's

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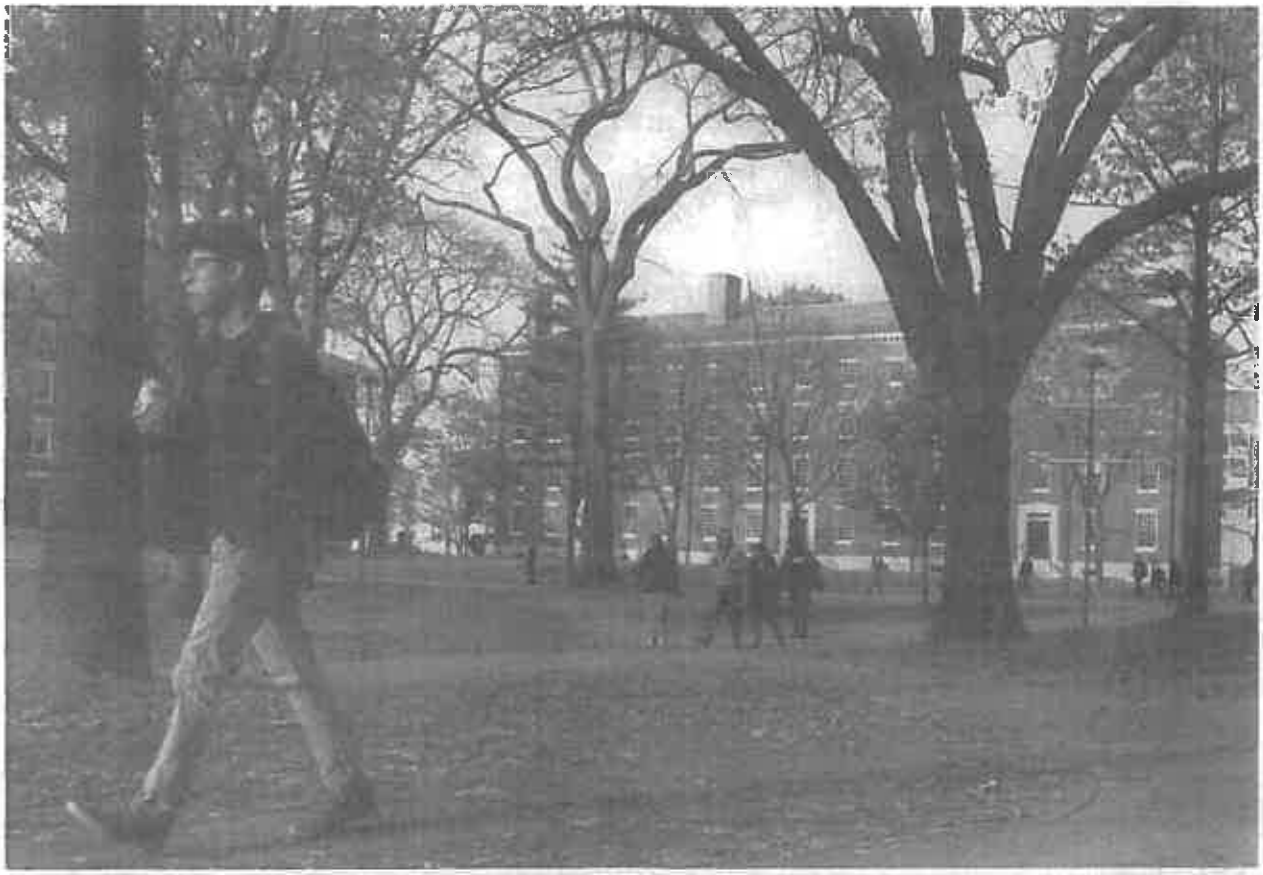
Rubella. These studies are still at a preliminary phase and the refinement of vaccine preparations which can be used in clinical practice will require a lengthy period of time and will be at high costs. .D. Vinnedge, *The Smallpox Vaccine*, The National Catholic Bioethics Quarterly, Spring 2000, vol.2, no. 1, p.12. .G.C. Woodrow, *An Overview of Biotechnology As Applied to Vaccine Development*, in «*New Generation Vaccines*», G.C. Woodrow, M.M. Levine eds., Marcel Dekker Inc., New York and Basel, 1990, see pp.32-37. W.M. McDonnell, F.K. Askari, *Immunization*, JAMA, 10th December 1997, vol.278, no.22, pp.2000-2007, see pp. 2005-2006.

[14] Such a duty may lead, as a consequence, to taking recourse to "objection of conscience" when the action recognized as illicit is an act permitted or even encouraged by the laws of the country and poses a threat to human life. The Encyclical Letter *Evangelium Vitae* underlined this "obligation to oppose" the laws which permit abortion or euthanasia "by conscientious objection" (no.73)

[15] This is particularly true in the case of vaccination against German measles, because of the danger of Congenital Rubella Syndrome. This could occur, causing grave congenital malformations in the foetus, when a pregnant woman enters into contact, even if it is brief, with children who have not been immunized and are carriers of the virus. In this case, the parents who did not accept the vaccination of their own children become responsible for the malformations in question, and for the subsequent abortion of foetuses, when they have been discovered to be malformed.

own children but also, and perhaps more specifically, for the health conditions of the population as a whole – especially for pregnant women;
- the lawfulness of the use of these vaccines should not be misinterpreted as a declaration of the lawfulness of their production, marketing and use, but is to be understood as being a passive material cooperation and, in its mildest and remotest sense, also active, morally justified as an *extrema ratio* due to the necessity to provide for the good of one's children and of the people who come in contact with the children (pregnant women);
- such cooperation occurs in a context of moral coercion of the conscience of parents, who are forced to choose to act against their conscience or otherwise, to put the health of their children and of the population as a whole at risk. This is an unjust alternative choice, which must be eliminated as soon as possible.

Harvard mumps outbreak grows to 40 cases



REUTERS/FILE

The mumps outbreak at Harvard University has tripled in size since mid-March, with 40 cases confirmed since the beginning of the year, according to the state Department of Public Health.

By Felice J. Freyer | GLOBE STAFF APRIL 26, 2016

As of April 1, the US Centers for Disease Control and Prevention reported 467 mumps cases nationwide, but did not delineate how many were at universities.

Zoback said the infected students had all been vaccinated against mumps, as required by law. It's possible the vaccine didn't work in some people, or that the virus mutated in ways that made the shot less effective. The mumps vaccine fails to induce immunity in about 12 percent of people who receive it, so mumps outbreaks occur occasionally even in highly vaccinated populations.

"This shows the importance of both personal protection and immunization," Zoback said. "Immunization prevents a wider outbreak when we see periodic increases like this."

Mumps is spread through saliva — by coughing or sneezing; sharing utensils or cups; or handling objects touched by a sick person. Harvard has been urging students to wash hands frequently.

Barreira told the Crimson that students must "take seriously that they shouldn't be infecting one another. . . . The concern is that if there's a spike this week, that means those students expose others, so now we're looking at a potential serious interruption to commencement for students. Students will get infected, and then go into isolation."

Mumps cases have also been reported at Boston University, the University of Massachusetts Boston, Tufts University, and Bentley University, as well as colleges and universities in other states.

A mumps outbreak at Harvard University has tripled in size since mid-March, with 40 cases confirmed since the beginning of the year, according to the state Department of Public Health.

As of Monday, 11 students remained in isolation, said university spokeswoman Lindsey Baker.

This year's Harvard outbreak tops the last big mumps cluster in Massachusetts, when 39 confirmed and probable cases were recorded at Boston College in 2013.

The Harvard Crimson reported Tuesday that Dr. Paul J. Barreira, director of Harvard University Health Services, expressed worries the outbreak might affect commencement.

But Baker said Harvard does not expect to make changes to its commencement plans because of the illnesses. Barreira was merely cautioning that individual students may miss out on the graduation ceremony and other end-of-semester activities if they become ill and have to be isolated, she said.

Although mumps cases have been reported at other universities, Harvard is the only one with such large numbers, said Scott Zoback, spokesman for the state health department.

Statewide, 67 cases have been reported since the beginning of the year, he said.

For example, Indiana health officials have confirmed 22 mumps cases at Indiana University in Bloomington, 24 at Butler University in Indianapolis, five at Indiana University-Purdue University Indianapolis, and eight at Purdue University in West Lafayette.

Mumps symptoms include puffy cheeks or jaws from swollen salivary glands, as well as fever, headache, muscle aches, and fatigue.

Felice J. Freyer can be reached at felice.freyer@globe.com.

Whooping Cough Cases on the Rise

By Matt McCullock | mmccullock@kfdx.com (mailto:mmccullock@kfdx.com)

Published 08/10 2015 04:37PM Updated 08/10 2015 06:21PM WICHITA FALLS, TX

Officials with the Wichita Falls-Wichita County Health District are wondering why whooping cough numbers are on the rise with reports of 13-cases of pertussis in children since January of this year.

"I guess it's just our turn to have the whooping cough," Wichita County nursing administrator, Lynette Williams said.

"All of the kids that have had it have been immunized, and so we're not really sure where they're getting it from," Williams said. "This summer we've seen an increase in it so we're trying to figure out what's going on and make sure everyone gets their immunizations before school starts."

Deborah Booher is in charge of investigating and identifying diseases in the county.

She has noticed a trend with the infection.

"I noticed in 2012, there was 14-cases in Wichita County," Booher said. "It seems like according to my Epidemiology Red Book, every three to four years pertussis is an epidemic even though we get vaccinations and our children get vaccinated, it still makes the rounds in any given area at any given time."

She says that a lot of times, children don't realize they have the infection.

"The thing I've heard with the older kids is ,'Oh well she just had this cough for a few days and finally I just decided to take her to the ER. She never ran a fever, felt bad and still went here or there and then they find out they had it," Booher said.

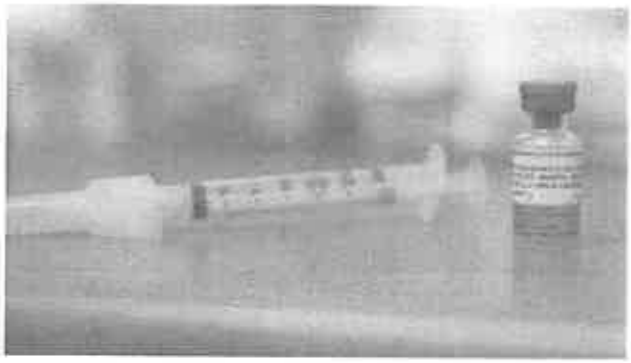
So if you suspect your child has been exposed to whooping cough, don't hesitate to take them to the doctor--especially with the start of the upcoming school year right around the corner.

If you would like your child to get vaccinated for pertussis, you can visit your family physician or bring them to the Health District.

6 University of Missouri students confirmed with mumps

POSTED 5:34 AM, JULY 28, 2015, BY ASSOCIATED PRESS

This is an archived article and the information in the article may be outdated. Please look at the time stamp on the story to see when it was last updated.



COLUMBIA, Mo. (AP) _ Lab results have confirmed that six University of Missouri students came down with the mumps, while a seventh suspected case came back negative.

The Columbia Daily Tribune reports the Columbia/Boone County Department of health and Human Services expects lab results for four more suspected cases by the end of the week.

Test results confirmed five mumps cases last week. Health department spokeswoman Andrea Waner says those five and the newest confirmed case all are university students who have had two doses of the mumps, measles and rubella (MMR) vaccine.

The seventh case that tested negative also is a University of Missouri student.

Waner says most people recover fully within a few weeks and serious complications

from mumps are rare.

—

Information from: Columbia Daily Tribune

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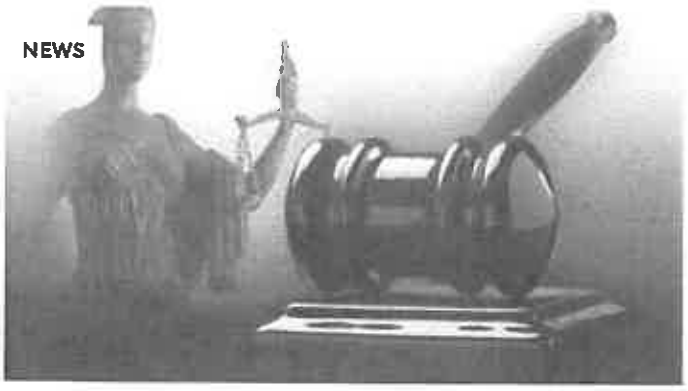

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Kevin Vesey Aug 1, 2016, 5:57 pm Aug 1, 2016, 5:59 pm

Mumps outbreak sweeps Long Beach; affected residents had already been vaccinated

18 people known to have contracted the disease; health officials say more cases possible

When most people hear about the mumps, they usually think of it as a disease that nobody catches anymore.

But according to Nassau County health officials, 18 people in the Long Beach area have come down with the once common infection, best known for causing swelling along the jawline.

County Health Commissioner Dr. Lawrence Eisenstein tells us that of the 18 confirmed cases, most patients are between the ages of 19 and 30. A few, however, are in their 50s.

The patients came down with symptoms over the last few days – despite having already been vaccinated.

"Sometimes nature throws a strain at us that might have mutated a little bit, and coverage of the vaccine is not 100 percent," Eisenstein explained.

Aside from its trademark swelling, the mumps also causes a headache, fever and pains.

There's no treatment. The mumps usually clears up on its own.

If you think you're sick with the mumps, officials say you should call your doctor right away and call your boss to say you're not going to work.

"Since there is no cure, the most important thing is, if you're sick and you have mumps, please stay home for five days," Eisenstein says.

People with the mumps should cover their mouths when they cough or

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sneeze, and avoid sharing drinks or kissing.

The health department says they could see a few more cases pop up before the outbreak starts to die down.

TAGS Long Island | News | Health | Long Beach | FIOS1 News Now | Kevin Vesey | Dr. Lawrence Eisenstein | Mumps | Outbreak

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Measles Outbreak Traced to Fully Vaccinated Patient for First Time

By Nsikan Akpan | Apr. 11, 2014 , 12:00 PM

Get the measles vaccine, and you won't get the measles—or give it to anyone else. Right? Well, not always.

Contagious. Measles vaccination rates top 90% in high-density cities like New York, but new data suggest even the immunized can catch and spread the disease. NYCstocker/iStockphoto/Thinkstock. (Inset) Dr Heinz F. Eichenwald/CDC

A person fully vaccinated against measles has contracted the disease and passed it on to others. The startling case study contradicts received wisdom about the

vaccine and suggests that a recent swell of measles outbreaks in developed nations could mean more illnesses even among the vaccinated.

When it comes to the measles vaccine, two shots are better than one. Most people in the United States are initially vaccinated against the virus shortly after their

even if a fully vaccinated person does become infected —a rare situation known as "vaccine failure"—they weren't thought to be contagious.

That's why a fully vaccinated 22-year-old theater employee in New York City who developed the measles in 2011 was released without hospitalization or quarantine. But like Typhoid Mary, this patient turned out to be unwittingly contagious. Ultimately, she **transmitted the measles to four other people**, according to a recent report in *Clinical Infectious Diseases* that tracked symptoms in the 88 people with whom "Measles Mary" interacted while she was sick. Surprisingly, two of the secondary patients had been fully vaccinated. And although the other two had no record of receiving the vaccine, they both showed signs of previous measles exposure that should have conferred immunity.

A closer look at the blood samples taken during her treatment revealed how the immune defenses of Measles Mary broke down. As a first line of defense against the measles and other microbes, humans rely on a natural buttress of IgM antibodies. Like a wooden shield, they offer some protection from microbial assaults but aren't impenetrable. The vaccine (or a case of the measles) prompts the body to supplement this primary buffer with a stronger armor of IgG antibodies, some of which are able to neutralize the measles virus so it can't invade cells or spread to other patients. This secondary immune response was presumed to last for decades.

By analyzing her blood, the researchers found that Measles Mary mounted an IgM defense, as if she had never been vaccinated. Her blood also contained a potent arsenal of IgG antibodies, but a closer look

Science Insider

Ornithologists set their nets in Washington, D.C.—to catch birds and attention

BY DAVID MALAKOFF | AUG. 5, 2016

revealed that none of these IgG antibodies were actually capable of neutralizing the measles virus. It seemed that her vaccine-given immunity had waned.

Although public health officials have assumed that measles immunity lasts forever, the case of Measles Mary highlights the reality that "the actual duration [of immunity] following infection or vaccination is unclear," says Jennifer Rosen, who led the investigation as director of epidemiology and surveillance at the New York City Bureau of Immunization. The possibility of waning immunity is particularly worrisome as the virus surfaces in major U.S. hubs like **Boston**, **Seattle**, New York, and the **Los Angeles area**. Rosen doesn't believe this single case merits a change in vaccination strategy —for example, giving adults booster shots—but she says that more regular surveillance to assess the strength of people's measles immunity is warranted.

If it turns out that vaccinated people lose their immunity as they get older, that could leave them vulnerable to measles outbreaks seeded by unvaccinated people—which are increasingly common in the United States and other developed countries. Even a vaccine failure rate of 3% to 5% could devastate a high school with a few thousand students, says Robert Jacobson, director of clinical studies for the Mayo Clinic's Vaccine Research Group in Rochester, Minnesota, who wasn't involved with the study. Still, he says, "The most important 'vaccine failure' with measles happens when people refuse the vaccine in the first place."

Posted in. **Health**

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Measles

In December 2014, a large outbreak of measles started in California when at least 40 people who visited or worked at Disneyland theme park in Orange County contracted measles; the outbreak also spread to at least half a dozen other states. On April 17, 2015, the outbreak was declared over, since at least two 21-day incubation periods (42 days) have elapsed from the end of the infectious period of the last known outbreak-related measles case.

Measles is a highly contagious viral disease. It is widespread in many parts of the world, including Europe, Africa, and Asia. Measles begins with a fever that lasts for a couple of days, followed by a cough, runny nose, conjunctivitis (pink eye), and a rash. The rash typically appears first on the face, along the hairline, and behind the ears and then affects the rest of the body. Infected people are usually contagious from about 4 days before their rash starts to 4 days afterwards. Children routinely get their first dose of the MMR (measles, mumps, rubella) vaccine at 12 months old or later. The second dose of MMR is usually administered before the child begins kindergarten but may be given one month or more after the first dose. For anyone planning to travel internationally, the California Department of Public Health (CDPH) strongly encourages all Californians to make sure they are protected against measles and other dangerous diseases before they go abroad.

For additional information on California measles cases, please see the Measles Surveillance Updates.

How Well-Vaccinated Is Your Child's Child Care Facility/School?

Child care facilities with low vaccination rates are at increased risk for outbreaks of vaccine-preventable diseases. Some children are allowed by California law to skip immunizations if a parent submits a personal beliefs exemption (PBE) or medical exemption (PME) at enrollment. Other children, may be admitted to child care on the 'condition' they complete remaining vaccinations when due. Often there is no follow-up and these children remain under-vaccinated. To lookup vaccination rates at your child care/ school, click below:

Child Care/Preschool | Kindergarten | 7th Grade

Facts

Measles FAQs
Disease and vaccine information from the Centers for Disease Control.

Measles Images
Color images from the CDC.

Information for Health Professionals

Measles Clinical Guidance
Identification, Testing and Isolation of Suspect Measles Cases

Statewide CDPH/LHD measles outbreak update Feb 3 2015 (PowerPoint, new window)

CDPH Measles Investigation Quick Sheet (PDF, New Window)
Concise guide for local health department disease investigation of measles.

Measles Source Identification Worksheet (Word, New Window)
Measles source identification worksheet for cases without an obvious source of infection (Updated March 2014).

Prevention and Control

Measles Contact Interview Form (Word, New Window)

Put Measles on the Spot Poster (PDF, New Window)

Measles Alert Poster: Tell Staff and Get a Mask (PDF, New Window)

MMR Vaccine Information Statements in Several Languages (CDC)

School Measles Exposure Letter Template (Word, New Window)

School Measles Exposure Letter Template en Español (Word, New Window)

Resources

CDC Manual for the Surveillance of Vaccine-Preventable Diseases
Information about measles including laboratory testing, surveillance and outbreak control.

Immunization Branch, California Dept. of Public Health

Measles - CDC Pink Book (PDF, New Window)
A twenty page document with information about the disease and vaccine.

CDPH HC Facility Infection Control for Suspect Measles Patients (PDF, New Window)
Measles Infection Control in Health Care Facilities.

Measles Alert Poster for Clinicians (PDF, New Window)
Poster to remind clinicians to consider measles when they see a rash illness.

CDPH Measles Laboratory Testing (PDF, New Window)
Specimen collection and laboratory test interpretation.

CDPH-VRDL Guidelines for Laboratory Services
Guidelines for laboratory services offered by the CDPH Viral and Rickettsial Diseases Laboratory.

Blood Specimen Collection Using Capillary Tubes (PDF, New Window)
Instructions on collecting a blood specimen for testing using capillary tubes.

Measles Specimen Collection Using Capillary Tubes (PDF, New Window)
Poster presented at American Public Health Association (APHA) meeting after Measles outbreak in San Diego, 2008.

ACIP Recommendations for the MMR Vaccine
Vaccine use and strategies for measles elimination.

IG for the Prophylaxis of Measles (PDF, New Window)
CDPH recommendations for the use of immune globulin (IG) for the prophylaxis of measles

Data and Surveillance

Vaccine Preventable Disease Reports
The Immunization Branch collects and publishes information on vaccine-preventable diseases in California. This page includes the most recent reports as well as information on when and how to report VPD cases.

Measles Surveillance Updates

Forms

Measles Case Report Form

CDC Vaccine Preventable Diseases
A large collection of Web pages about the prevention of communicable diseases.

Measles Educational Resources

Español (Spanish)

Vacunas Y Mi Salud

Casos de Sarampión Aumentan en California

Sarampión INFO

Last modified on: 2/2/2016 9:24 AM

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State of California—Health and Human Services Agency
California Department of Public Health

KAREN L. SMITH, MD, MPH
Director and State Health Officer

EDMUND G. BROWN JR.
Governor

July 2, 2015

TO: Interested Parties

FROM: Sarah Royce, M.D., M.P.H, Chief
Center for Infectious Diseases
Division of Communicable Disease Control, Immunization Branch

SUBJECT: **Senate Bill 277**

Governor Brown signed Senate Bill (SB) 277 on June 30, 2015. Effective one year from now in July 2016, SB 277 will:

- No longer permit immunization exemptions based on personal beliefs for children in child care and public and private schools;
- Permit personal belief exemptions submitted before January 1, 2016 to remain valid until a pupil reaches kindergarten or 7th grade;
- Remove immunization requirements for:
  - Students in home-based private schools
  - Students enrolled in an independent study program who do not receive classroom-based instruction
  - Access to special education and related services specified in an individualized education program

  Students in the above categories will still need to provide immunization records to their schools before entry, and schools will still need to report to the California Department of Public Health (CDPH) the immunization status of all students at the existing checkpoints of child care, kindergarten and 7th grade;
- Allow medical and personal beliefs exemptions from any new immunization requirement initiated by CDPH for attendance at school or child care.

Additional information about the implementation of SB 277 will become available by 2016.

The language of SB 277 is available at
https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201520160SB277.

The Governor's signing message is available at
http://gov.ca.gov/docs/SB_277_Signing_Message.pdf.

Immunization laws currently in effect may be found at
http://www.shotsforschool.org/immunizationlaws/.

CCLHO
CALIFORNIA CONFERENCE OF LOCAL HEALTH OFFICERS

DEPARTMENT OF PUBLIC HEALTH

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Leah Northrop, MPA, MAIS
Executive Administrator
Leah.Northrop@cdph.ca.gov

Board of Directors
Sacramento, CA
Meeting Minutes
February 4, 2016

ATTENDEES:

Janet Berreman, MD, City of Berkeley
Cameron Kaiser, MD, Riverside
Karen Milman, MD, Sonoma
Ken Cutler, MD, Nevada
Rob Oldham, MD, Placer
Ed Moreno, MD, Monterey
Eric Handler, MD, Orange
Matthew Willis, MD, Marin
Karen Smith, MD, CDPH/Director
Gil Chavez, MD, CDPH/CID
Julie Nagasako, CDPH/Fusion Center
Valerie Quinn, CDPH/Tobacco Control
Latesa Slone, CDPH/Fusion Center
Jerry Jeffe, CA Chronic Care Coalition
Leah Northrop, CDPH/CCLHO
Connie Caldwell, MD, Mendocino
Karen Relucio, MD, San Mateo
Lou Anne Cummings, MD, Sutter
Muntu Davis, MD, Alameda
John Walker, MD, Stanislaus
Nancy Williams, MD, El Dorado
Alvaro Garza, MD, San Joaquin
Robert Kim-Farley, MD, Los Angeles
James Watt, MD, CDPH/CID/DCDC
Sarah Royce, MD, CDPH/Immunization Branch
Fabian Perez, CDPH/OHE
Gordon Sloss, CDPH/CDIC
Katya Ledin, CAPHLD
Kat DeBurgh, HOAC
Ashley Barbosa, CDPH/CCLHO

ON THE PHONE/: COMPUTER

Ron Chapman, MD, Yolo
Liza Ortiz, MD, Tuolumne
Karen Tait, MD, Lake
Scott Morrow, MD, San Mateo
Rita Kerr, MD, Amador
Andrew Deckert, MD, Shasta
Bela Matyas, MD, Solano
Robert Levin, MD, Ventura
Megan Crumpler, Riverside, CAPHLD
John Holguin, Long Beach, CACDC
Edith Cabusley, San Mateo,CCLHDHE
Robin Cox, Solano, CCLDHE
Michael Mudgett, CHIRB
Rob Schechter, CDPH/Immunization Branch
Rick Johnson, MD, Alpine/Inyo/Mono
Charity Dean, MD, Santa Barbara
Karen Haught, MD, Tulare
Wilma Wooten, MD, San Diego
Penny Borenstein, MD, San Luis Obispo
Olivia Kasirye, MD, Sacramento
Max Ohikhuare, MD, San Bernardino
Julie Vaishampayan, MD, San Joaquin
Barbara Cole, Riverside
Eric McDonald, San Diego,CACDC
Judith Thigpen, CTCA
Pam Dudley, DPHN, San Luis Obispo
George Flores, TCE
Karen Ramstrom, CDPH/CDIC

TIME	SUBJECT / AGENDA	DISCUSSION	ACTION
9:00 a.m.	**Introductions and Welcome/President's Report**	Janet Berreman, MD, MPH, President, California Conference of Local Health Officers (CCLHO) and Health Officer, City of Berkeley, began the meeting by giving the President's report and then asking attendees to introduce themselves. ▪ The CCLHO 2015 Accomplishments document is being finalized and should be available for review at the March Board meeting. ▪ The first meeting of the CCLHO Health Equity and Social Determinants of Health Workgroup will be meeting today after the Board meeting. ▪ The CCLHO Spring Conference planning is coming along nicely and a location for the Fall Conference is being finalized. It will most likely be in Los Angeles County on the eastern side near San Bernardino or Pomona. The preferred dates being considered are October 5-7, 2016. ▪ The Executive Committee discussed with CDPH violence prevention, Zika Virus planning, metrics used for the indicators for Let's Get Healthy, local access to FITNESSGRAM data, SB 277 implementation, TB prevention, Medi-Cal Managed Care providers and medical directors. ▪ SJR 20 is on lifting the Federal funding ban on gun violence research. This funding ban has been in place for a number of years and many did not know it existed. ▪ The Public Health Institute would like CCLHO to sign onto a concept paper. It was brought to the group by Dr. Lynn Silver. The paper is an effort to initiate public conversation that a Wellness Fund to support prevention work is a good idea. The paper is 4 pages and is very high level. The Executive Committee was in support with 2 caveats. One is acknowledging that this is a very broad and conceptual paper and the other is clarifying that the Wellness Fund proposes new funding and not funding that is already going to public health and prevention efforts. ▪ Form 700's are due April 1, 2016 for CCLHO members. Please fill them out and return them to the CCLHO office.	**1. MOTION CARRIED**: Motion to approve the CCLHO January 7, 2016 Board meeting minutes carried. (see attachment for tallied votes) **2. ACTION:** CCLHO recommends Senate support on lifting the Federal funding ban on gun violence research. (see attachment for tallied votes) **3. ACTION:** CCLHO supports signing onto the concept paper with the Public Health Institute with 2 caveats. One is acknowledging that this is a very broad and conceptual paper and the other is clarifying that the Wellness Fund proposes new funding and not funding that is already going to public health and prevention efforts. (see attachment for tallied votes)
9:15 a.m.	**California Department of Public Health (CDPH) Report**	Karen Smith, MD, MPH, Director and State Public Health Officer, California Department of Public Health (CDPH), reported. ▪ CDPH has received many requests in relation to Zika Virus, including setting up a hotline. Dr. Smith has pushed back because the best thing for the public to do is call their local health officer so they can explain what is going on in that	

TIME	SUBJECT / AGENDA	DISCUSSION	ACTION
		jurisdiction and what resources are available there. If it does become overwhelming for locals, CDPH will reconsider the idea. Right now, it has become more a media thing because California has only had 2 cases and they were both recent travelers. CDPH will be doing an all Legislature call because they have been receiving many calls from elected officials and that may assist with deflecting them from local health officers. Dr. Kim-Farley commended CDPH staff and their response to Zika Virus. Dr. Kim-Farley commented on sitting back and waiting while the vector is here in California and hopes more prevention planning can be done. Dr. Smith has been looking into Vector Control and has a meeting planned with them soon. Dr. Walker really enjoyed the call with CDPH and suggested holding a similar call with healthcare partners so there can be a common message to hospitals. Dr. Walker also noted that most travel advisories have too much information. Stanislaus County is looking at putting together a simple 1-2 pager/poster in both English and Spanish. Dr. Moreno suggested to Dr. Smith when she meets with Vector Control to suggest what was done in Fresno County. Districts who have an upcoming election can ask residents to reassess their services and either choose to continue or enhance services within the LHD. During West Nile, a district in Fresno County was up for an appropriation ballot and agreed to assess themselves and how many residents received services from public health. Highlighting West Nile and now Zika can start the conversation. They can also expand districts to cover these services because in some areas, one side of the street is being covered where the other is not. Dr. Johnson commented on the Zika Virus call with CDPH that Susan Fanelli noted Ebola Funding. There has been a 9 month Federal extension until June of 2017. Some of the funds can be used for Zika response and vector borne control agencies. Dr. Smith commented that Ms. Fanelli is trying to work with CDC to get them to decide what exactly can be done with the funding. Dr. Cutler asked about laboratory capacity given there is no commercial option in relation to Zika Virus. Dr. Smith will be meeting with Dr. Chavez and the laboratories to discuss a screening and submission form. ▪ CDPH is still working on getting a new Director for the Center for Chronic Diseases because they had to shift course with some items that came up with CalHR. ▪ Dr. Smith met with Medi-Cal Managed Care Providers about TB and the need to streamline diagnostics. She also mentioned putting all of the first and second line TB drugs on their formularies. The providers asked really great questions, so it seemed as though 'they got it' but what they did not seem to get was that there was a health department in their jurisdictions and that they could help. They also did not know that some LHJ's have TB Control programs that they	

TIME	SUBJECT / AGENDA	DISCUSSION	ACTION
		could work with. Dr. Smith noted that this would be a great time for Health Officers to reach out the Directors of their Medi-Cal Managed Care Health Plans to initiate a relationship with them. Dr. Smith also let them know that they could always call the CDPH TB Branch. Next time Dr. Smith meets with them, they will discuss immunizations. Dr. Berreman asked that Dr. Smith share with CCLHO the talking points and "ask" of what she brings to those meetings so that locals can utilize the information as well to spark conversation. ▪ CDPH has been reluctant to provide guidance on SB 277 implementation because they do not have experience with the Individualized Education Program (IEP) statute. The Department of Education has also been reluctant and CDPH will meet with them again soon to see if they can provide some level of guidance. ▪ Dr. Handler asked for Dr. Smith's thoughts on the CMA backing the legalization of recreational marijuana. Dr. Smith was unaware they had made that claim. CDPH has been deeply involved in the implementation of the Medical Marijuana Regulation and Safety Act. Julie Nagasako, Let's Get Healthy California Coordinator, Fusion Center, CDPH, presented. ▪ Ms. Nagasako walked the group through the Let's Get Healthy California Website and highlighted different pages. ▪ Are all of the data sources highlighted available at the county level? Many are available but some indicators are only available at the State level. ▪ What is the data source? The sources of all the data are available in the "Metadata" section. ▪ How can someone search for information that is not an indicator? If you type in "breastfeeding" into the search bar, it will still pull up 70 articles.	
10:00 a.m.	**SB 277 Implementation and Health Officer Roles**	Sarah Royce, MD, MPH, Chief, and Robert Schechter, MD, Medical Officer; Immunization Branch, CDPH, presented. ▪ See presentation. ▪ **Discussion:** Opposition to this will be finding ways to get around the requirements. Some parents may take their children out of school for first or eighth grade if that is when they will be getting checked. Local jurisdictions need to work together and be consistent in their response. Kindergarten is not mandatory in California; the law says children have to be in school by the age of 6. Another issue that may arise is who at the school is responsible for checking the records. The consensus of the group was to have a uniform approach in the response to this. The CCLHO Executive Committee will work on drafting a communication to CDPH and bring it back to the Board for comments.	

TIME	SUBJECT / AGENDA	DISCUSSION	ACTION
10:35 a.m.	**Committee Reports and Action Items** ▪ **Communicable Disease Control and Prevention (CDCP) Committee** ▪ **Chronic Disease Control Committee** ▪ **Environmental Health Committee** ▪ **Health Information and Data Committee** ▪ **Small Jurisdiction Committee**	Robert Kim-Farley, MD, Los Angeles County and Barbara Cole, RN, PHN, MSN, Riverside County, reported. ▪ The next CDCP Committee meeting will be held in Sacramento on February 18. Topics on the agenda include updated guidance on health care facilities on traveling screenings, immunization requirements for foster parents, the clean-up of the California Health and Safety Code in an omnibus bill. ▪ See Committee Action Items Submission Form. Wilma Wooten, MD, MPH, Health Officer, San Diego County, reported. ▪ The next meeting will be held on March 3 in Sacramento ▪ The CCLHO/CHEAC Chronic Disease Leadership Project met in Sacramento last week. Dr. Paul Simon is the new co-chair along with Mary Anne Morgan. Ed Moreno, MD, MPH, Health Officer, Monterey County, reported. ▪ The Environmental Health Committee meeting scheduled for last week is in the process of being rescheduled. Topics for the next meeting include grey water use and reuse, diversion of food and organized camps. Bela Matyas, MD, MPH, Health Officer, Solano County, reported. ▪ The next Health Information and Data Committee will meet on April 6. Ken Cutler MD, MPH, Health Officer, Nevada County, reported. ▪ The next SJC meeting will be held on February 9, 2016. Topics to be discussed include the delay in finding psychiatric beds for 51/50 patients and the impact at local jails. Dr. Jessica Nunez de Ybarra will be discussing chronic disease capacity at the local level and how to align with the state.	**4. ACTION:** CCLHO accepted the proposed changes for Title 17 section 2500 and 2505 as provided. (see attachment for tallied votes)
11:15 a.m.	**California Tobacco Control Program Counter E-Cigarette Ad Campaign**	Valerie Quinn, M.Ed., Communications/Media Strategist, California Tobacco Control Program, CDPH, presented. ▪ See presentation.	
11:50 a.m.	**Legislative Updates: Health Officers Association of California (HOAC)**	Kat DeBurgh, MPH, Executive Director, HOAC reported. ▪ See presentation. ▪ HOAC will be hosting their Spring Continuing Medical Education Program at the Spring Semiannual Meeting in Berkeley on April 14-15, 2016. ▪ There will be a Health Happens Aqui Training on March 7th, 2016 which is part of HOAC's Communication Training with TCE. Every jurisdiction is entitled to one complimentary registration with travel assistance. Ms. DeBurgh has reached out to all health officers and CHEAC representatives with the information. There are 36 slots available for others who would like to participate and 5 of those spots are still available. The cost to reserve an additional spot is	

TIME	SUBJECT / AGENDA	DISCUSSION	ACTION
		$17.00.	
12:25 p.m.	**Brief Reports** **Volunteers to Advisory Committees** **Affiliates**	See reports: ▪ Drinking Water Program Transition Advisory Group ▪ Advisory Group on Feasibility of Developing Criteria for Direct Potable Reuse ▪ CDPH Office of Health Equity ▪ Joint Advisory Committee (JAC) on Public Health Emergency Preparedness-CDPH and EMSA See report: ▪ CCLHDN	
12:55 p.m.	**Public Comment**	None	
1:00 p.m.	**Adjourn**	The next CCLHO Board Meeting will be held on March 3, 2016 in Sacramento.	

Attachment 1

CCLHO Board of Directors
February 3, 2016
Tallied Votes

Health Officer	1. Action	2. Action	3. Action	4. Action
	Approval of minutes	Senate support of lifting Federal ban on gun violence research	Signing onto concept paper with PHI	Accepting proposed changes for Title 17 section 2500 and 2505
C. Kaiser	Y	Y	Y	Y
N. Williams	Y	Y	Y	Y
K. Cutler	Y	Y	Y	Y
E. Moreno	Y	Y	Y	Y
R. Oldham	Y	Y	Y	Y
L. Cummings	Y	Y	Y	Y
M. Lundberg	Y	Y	Y	Y
J. Berreman	Y	Y	Y	Y
K. Milman	Y	Y	Y	Y
K. Relucio	Y	Y	Y	Y
J. Walker	Y	Y	Y	Y
C. Caldwell	Y	Y	Y	Y
M. Willis	Y	Y	Y	Y
M. Davis	--	--	Y	Y
E. Handler	--	--	--	Y
A. Garza	--	--	--	Y
Total-16	**Y-13** **N-0** **A-0**	**Y-13** **N-0** **A-0**	**Y-14** **N-0** **A-0**	**Y-16** **N-0** **A-0**

Y - Yay
N - Nay
A - Abstention
-- Not present during vote

EXHIBIT 9
Page 106

Attachment 2
Acronym List

AB Assembly Bill
AIDS Acquired Immune Deficiency Syndrome

AMA	American Medical Association
ARB	Air Resources Board
CACDC	California Association of Communicable Disease Controllers
CAL/OSHA	Division of Occupational Safety and Health (Dept. of Industrial Relations)
CAPHLD	California Association of Public Health Laboratory Directors
CCLAD	California Conference of Local AIDS Directors
CCLHO	California Conference of Local Health Officers
CCLHDME	California Conference of Local Health Data Managers and Epidemiologists
CCR	California Code of Regulations
CD	Communicable Disease
CDC	Centers for Disease Control and Prevention
CDCP	Communicable Disease Control and Prevention
CDPH	California Department of Public Health
CHEAC	County Health Executives Association of California
CHHS	California Health and Human Services Agency
CHSI	Center for Health Statistics and Informatics
CID	Center for Infectious Diseases
CMMI	Centers for Medicare and Medicaid Innovation
CMS	Centers for Medicare & Medicaid Services
CTCA	California Tuberculosis Controllers Association
DPHN	Directors of Public Health Nursing
EHR	Electronic Health Record
EMS	Emergency Medical Services
EMSA	Emergency Medical Services Authority
EPO	Emergency Preparedness Office
PHAB	Public Health Accreditation Board
HIV	Human Immunodeficiency Virus
IT	Information Technology
LEMSA	Local Emergency Medical Services Agencies
LGHC	Let's Get Healthy California
LHD	Local Health Department
LHJ	Local Health Jurisdiction
OHE	Office of Health Equity
SB	Senate Bill
SJC	Small Jurisdiction Committee
STD	Sexually Transmitted Diseases
WIC	Women, Infants, and Children

SB 277 – Update
CCLHO - February 4, 2016

ShotsforSchool

Child Care | K-12 | 7TH Grade | College | Laws

▶SB277 FAQs

- Immunization Laws
- Exemptions
- ▶SB277 FAQs
- ▶Personal Beliefs Exemption FAQs
- Conditional Admission FAQs
- Handbook, Records, & Materials

ShotsForSchool > Immunization Laws > ▶SB277 FAQs

Senate Bill 277 Frequently Asked Questions

These FAQs were last updated on 11/13/2015 (this included edits to question 13).
This content is considered current until any future update is made.

Print file in English (PDF) | Spanish (PDF) | Russian (PDF)

Immunization Requirements for 2015

1. In 2015 and future years, which vaccines are required to enter child care or school in California?
2. In the summer or fall of 2015, are there any changes to the immunization requirements for children entering child care or school?

New law (SB277) for 2016 and future years

3. In 2016, what are the changes to the immunization requirements for children entering child care or school?
4. When does the law take effect?
5. Where can I review the new law?

SB 277 - Effective in 2016

- No new PBEs for current immunization requirements at child care or schools
- Specific PBEs for current pupils submitted before January 1, 2016 remain valid:
  - If in child care, until TK/Kindergarten
  - If in TK-6th grade, until 7th grade

SB 277 - Effective in 2016

- Removes immunization entry requirements for students who are in:
  - Home-based private schools
  - Independent study programs and do not receive classroom-based instruction
- Students in these categories still need to provide iz records to their schools before entry
- Schools will still need to report to CDPH the immunization status of all students in child care, Kindergarten and 7th grade.

Special Education Services

Under SB 277, the immunization requirements in California Health and Safety Code Section 120335 do "not prohibit a pupil who qualifies for an individualized education program, pursuant to federal law and Section 56026 of the Education Code, from accessing any special education and related services required by his or her individualized education program.

Special Education Services

- Students with IEPs continue to receive all special education and related services required in their IEPs regardless of the immunization requirements.
- Schools may consult with legal and policy resources at their Local Education Agencies regarding the implementation of IEPs as related to SB 277.
- CDPH continues to review SB 277 in consultation with CDE and CDSS.

"Related Services, as listed under IDEA, include…"

- Audiology services
- Counseling services
- Early identification and assessment of disabilities in children
- Medical services
- Occupational therapy
- Orientation and mobility services
- Parent counseling and training
- Physical therapy
- Psychological services
- Recreation
- Rehabilitation counseling services
- School health services
- Social work services in schools
- Speech-language pathology services
- Transportation

http://www2.ed.gov/parents/needs/speced/iepguide/index.html

IEP / IDEA – Placement decisions

- Least restrictive environment (LRE) requirements
  - To the maximum extent appropriate, children with disabilities must be educated with children who do not have disabilities
- "…Special classes, separate schools, or other removal from the regular educational environment may occur only if the child's disability is such that education in regular classes with the use of aids and services cannot be achieved satisfactorily.
- "Depending on the needs of the child, IEP may be carried out in the regular class, a special class (for some or all of the day), a special school, at home, in a hospital and institution, or in another setting

http://www2.ed.gov/parents/needs/speced/iepguide/index.html

Resources for LHDs

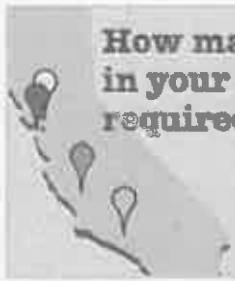
ShotsforSchool

Featured Questions

- Will all children with existing exemptions on file have to file a new form?
- Where is the immunization reporting login for school assessments?
- Questions About Immunizations, Tdap Requirement, PBEs and More

News

- New Law Eliminates Personal Belief Exemptions >>
- What is the Measles Vaccination Status in Your Child Care? Kindergarten?
- Get Your Children Up-to-Date on Vaccinations Before Back-to-School >>
- Emails from California Department of Public Heal



How many students in your school have required shots?

Child Care >
Kindergarten >
7th Grade >

Email

- For more information, email info@shotsforschool.org >
- View archived emails >

Immunization Reporting

Login and Instructions

Immunization Assessment Reporting Login >>

Tools

- California School Immunization Record (Blue Card)
- Guide to Immunizations Required Child Care | K-12
- Conditional Admission Immunization Schedule

New Laws

Personal Belief Exemptions

- New Law (SB 277) Effective in 2016 | FAQs | Spanish FAQs | Russian FAQs
- Summary of Current Law Expiring in 2016 (AB2109) | FAQs
- PBE Form (CDPH 8262) Spanish | Other Languages

Tdap for 7th Grade

- Summary of Law (AB 354)
- FAQs for Parents | Spanish
- FAQs for Schools and Providers
- Tools for Schools

▶SB277 FAQs

Immunization Laws
Exemptions
▶SB277 FAQs
▶Personal Beliefs Exemption FAQs
Conditional Admission FAQs
Handbook, Records, & Materials

ShotsForSchool > Immunization Laws > ▶SB277 FAQs

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New law (SB277) for 2016 and future years

3. In 2016, what are the changes to the immunization requirements for children entering child care or school?
4. When does the law take effect?
5. Where can I review the new law?
6. Which facilities are affected by the new law in 2016 and future years?

Personal Beliefs Exemptions Ending

7. In the new law on immunization requirements, are religious beliefs distinguished from other personal beliefs?
8. Will personal beliefs exemptions filed during or after 2016 be valid?
9. Will personal beliefs exemptions, including those based on religious beliefs, filed in California before 2016 remain valid in later years?
10. Is a personal beliefs exemption still valid if a child transfers between child-care facilities in California after 2015?

www.shotsforschool.org/k-12/how-doing/

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- Safest (95-100% of students fully vaccinated)
- Moderately Vulnerable (90-94.9% of students fully vaccinated)
- More Vulnerable(80-89.9% of students fully vaccinated)
- Most Vulnerable (less than 80.0% of students fully vaccinated)
- Delinquent (Failed to report in in 2014-15)*

Address or Zip Code: Sacramento 100mi

OR

School Name: Search

EXHIBIT 10
Page 118

Know Your Rights: Suspensions, Expulsions, and Involuntary Transfers

School Discipline: A Guide for Students & Parents

Leer en español »

What is suspension?

Suspension is a form of school discipline which temporarily removes you from a class or from school. Your school may prohibit you from school grounds, a classroom, or place you in a supervised ("in-school") suspension classroom separate from other students.

When can my school suspend me?

- **Your school cannot suspend you for just anything.** It can suspend you only for behavior explicitly listed in the California Education Code.
- **Your school cannot suspend you for school absences or tardiness.**
- **A school cannot suspend students below the fourth grade from school or place them in "in-school" suspension for "willful defiance."**
- **Your school may only suspend you for conduct related to a school activity or school attendance.** This includes conduct at school, during school-sponsored activities, and on your way to and from school.

What must my school do before it suspends me?

- **Your school must first try other interventions to change your behavior.** Your school may only suspend you after other interventions fail, unless your behavior is serious, violent, or dangerous to others.
- Other interventions can include conferences with your parents, referrals to counselors or psychologists, or anger management programs. School districts should also document the interventions they use.

What are my rights during the suspension process?

- **You have the right to an informal pre-suspension conference** with school or district staff, unless there is an emergency situation.
- **You have other rights during the process** including the right to tell your side of the story and present

evidence in the conference before you are suspended.

What are my rights after a final decision of suspension?

- Your school must send a written notice of its decision to your parents/guardians.
- Your school cannot suspend you for more than five days in a row or for more than 20 total school days in one school year.
- You may have the right to appeal your school's final decision.

What is expulsion?

Expulsion means your school district prevents you from attending traditional schools in your school district.

When can my school expel me?

- **Your school is required to expel you only for the following behaviors:** possessing or selling firearms, threatening another person with a knife, selling a controlled substance, attempting or committing a sexual assault, possessing an explosive, or inflicting serious bodily injury.
- **Your school may choose to expel you for other behavior, but only behaviors explicitly listed in the California Education Code.**
- Your school may expel you only for conduct on school grounds or at a school related activity off school grounds.
- **You cannot be expelled from your school for "willful defiance."**

What must my school do before it expels me?

- **You have the right to an expulsion hearing within 30 school days of the proposed expulsion.** Prior to your hearing, your district must continue to offer you an educational program. Your school district will make its final expulsion decision at your hearing.
- Your school district must provide you written notice of your expulsion hearing date at least ten days prior to your hearing.
- You have the right to request your student records and inspect evidence to be used against you before your expulsion hearing.

What are my rights during & after the expulsion process?

- **You have rights during your expulsion hearing,** including the right to bring advocates to help tell your side of the story.
- **You have rights after an expulsion hearing,** including the right to a written final decision, and the right to an appeal.
- If you win your hearing, you almost always have the right to return to your school.
- You may be eligible to return to your school district after expulsion. Check with your district for its process.

What is an involuntary transfer?

An involuntary transfer is when a school district transfers a student to an alternative school against the wishes of the student or their parent/ guardian. Schools have a lot of discretion in transfers, but there are important limits on their discretion. What are alternative schools? Alternative schools include county community schools, community day schools, and continuation schools. These schools may be beneficial for some students, but they often do not provide the same educational or extra-curricular opportunities as traditional schools.

What are my rights in involuntary transfers to county community schools?

- **You may be involuntary transferred to a county community school if you are expelled, referred by a School Attendance Review Board (SARB), or referred under court order.**
- **You may not be transferred to a county community school** solely because you are homeless or a foster youth.
- You have the right to object to your transfer to a county community school if the school cannot meet your educational needs, you have safety concerns, or if the school is geographically inaccessible.
- Your school district may not transfer you to a county community school that does not have enough space for you.
- If you are transferred to a county community school based on a SARB referral, you have the right to return to your original school or another traditional school at the end of the transfer period.

What are my rights in involuntary transfers to community day schools?

- **Your school district may only involuntary transfer you to a community day school if you are expelled, on probation, referred by a SARB, or referred through a district-level referral process.**
- You do not have a right to appeal your transfer to a community day school, but you can always appeal an expulsion that led to your transfer.

What are my rights if I am involuntarily transferred to a continuation school?

- **Your district may only involuntarily transfer you to a continuation school if you have committed a violation in the California Education Code, or you have had irregular attendance in your required classes.**
- Your district may not transfer you to a continuation school unless other attempts to change your behavior fail or your presence at school causes a danger to others or disrupts the instructional process.
- Your district may only transfer you to a continuation school in the semester when the act occurred or in the semester after.

What are my rights before and after a final decision to involuntarily transfer me to a continuation school?

- **You have the right to request a meeting with a representative of your superintendent before your involuntary transfer to a continuation school.** You have the right to present your side of the story with evidence, advocates, and witnesses.
- No one from your school may be involved in the final decision to transfer.
- You have the right to receive a written notice of your district's final transfer decision.
- You have the right to return to a traditional high school the following school year with consent of your school district superintendent.

Learn more

Leer en español »

For more detailed information on your rights and responsibilities during suspension, expulsion, and involuntary transfers, visit: www.aclunc.org/kyr If you are an English language learner, foster youth, or a student with a disability you have additional rights and protections.

Tools for achieving fair discipline

If you think your school is not complying with the law, please contact us.

Download this guide »

August 2016

Cajon Valley Union School District / Calendar

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18 First Day of School	19	20
21	22	23	24	25	26	27
28	29	30	31			

Loomis Union School District

July 2016 - June 2017

Instructional Calendar

Board Approved: June 16, 2016

Regular School Opening And Closing Dates

First Trimester:	Aug 11 - Nov 4	(59days)
Second Trimester:	Nov 7 - Mar 3	(63 days)
Third Trimester:	Mar 6 - June 2	(58 days)
		(180 days)

First day of School: August 11, 2016

Last day of School: June 2, 2017

Legal Holiday OBSERVED ◯ (per Ed Code 37220)

Independence Day - July 4, 2016 and July 4, 2017
Labor Day - September 5, 2016
Veterans Day - November 11, 2016
Thanksgiving - November 24, 2016
Christmas Eve -(Observed) December 23, 2016
Christmas - (Observed) December 26, 2016
New Year's Day - (Observed) December 30, 2016
Admission Day Observance- January 2, 2017
Dr. Martin Luther King, Jr. Day - January 16, 2017
President's Days - February 13 and 20, 2017
Memorial Day - May 29, 2017

STUDENT RECESSES

November 21-25, 2016
December 19, 2016 - January 3, 2017
April 10 - 14, 2017

Non-Student Days

Staff Development: 9/16, 10/28, 2/3, 3/10

Minimum days: ▽

4 Conference Days 11/15-17, 3/15

1 last day of school 6/2

6 Minimum days for staff development
11/4, 11/14, 12/16, 3/14, 4/24, 5/12

Report Cards Sent Home

November 16, 17, 18, 2016
March 15, 2017

MADERA UNIFIED SCHOOL DISTRICT

2016-17 Calendar (180 Days)

REVISED 7-26-16

Jul	4	Independence Day
Sep	5	Labor Day
Nov	11	Veterans' Day
Nov	24	Thanksgiving Day
Nov	25	Board-Declared Holiday
Dec	26	Board-Declared Holiday
Dec	27	Board-Declared Holiday
Jan	2	Board-Declared Holiday
Jan	3	Board-Declared Holiday
Jan	16	Martin Luther King Jr. Day
Feb	13	Lincoln's Day (Observed)
Feb	20	Washington's Day (Observed)
April	14	Good Friday
May	29	Memorial Day

THANKSGIVING BREAK
November 21 - November 25

WINTER RECESS
December 19 - January 6

SPRING RECESS
April 10 - April 14

Period	# Days
1	8/03/16 - 9/2/16 17
2	9/5/16 - 9/30/16 19
3	10/3/16 - 10/28/16 20
4	10/31/16 - 11/25/16 14
5	11/28/16 - 1/6/16 15
6	1/9/17 - 2/3/17 19
7	2/6/17 - 3/3/17 18
8	3/6/17 - 3/31/17 19
9	4/3/17 - 4/28/17 15
10	5/1/17 - 5/26/17 20
11	5/30/17 - 6/2/17 4
	Annual Total 180

1st Qtr - Aug 11 - Oct 7	41 days
2nd Qtr - Oct 10 - Dec 16	44 days
3rd Qtr - Jan 9 - Mar 16	48 days
4th Qtr - Mar 20 - June 2	48 days

NON - SCHOOL DAY
July 1 - August 10, 2016
March 10, 2017

FIRST DAY OF SCHOOL
August 11, 2016

LAST DAY OF SCHOOL
June 2, 2017

INSTITUTE DAYS
August 8, 2016
August 9, 2016
August 10, 2016

MUSD BOARD APPROVED: JULY 26, 2016
MOTION NO. 2-2016/17
DOCUMENT NO. 20-2016/17
7/26/16 1:39 PM

Placerville Union School District
2016-17 STUDENT CALENDAR

JUL '16

M	T	W	T	F
				1
4	5	6	7	8
11	12	13	14	15
18	19	20	21	22
25	26	27	28	29

AUG '16

M	T	W	T	F
1	2	3	4	5
[redacted]				12
15	16	17	18	19
22	23	24	25	26
29	30	31		

SEP '16

M	T	W	T	F
			1	2
5	6	7	8	9
12	13	14	15	16
19	[redacted]			
26	27	28	29	30

OCT '16

M	T	W	T	F
3	4	5	6	7
10	11	12	13	14
17	18	19	20	21
24	25	26	27	28
31				

NOV '16

M	T	W	T	F
	[redacted]			
7	8	9	10	11
14	15	16	17	18
21	22	23	24	25
28	29	30		

DEC '16

M	T	W	T	F
			1	2
5	6	7	8	9
12	13	14	15	[redacted]
19	20	21	22	23
26	27	28	29	30

JAN '17

M	T	W	T	F
2	3	4	5	6
9	10	11	12	13
16	17	18	19	20
23	24	25	26	27
30	31			

FEB '17

M	T	W	T	F
		1	2	3
6	7	8	9	10
13	14	15	16	17
20	21	22	[redacted]	
27	28			

MAR '17

M	T	W	T	F
		1	2	3
6	7	8	9	10
13	14	15	16	17
20	21	22	23	24
27	28	29	30	31

APR '17

M	T	W	T	F
3	4	5	6	7
10	11	12	13	14
17	18	19	20	21
24	25	26	27	28

MAY '17

M	T	W	T	F
1	2	3	4	5
8	9	10	11	12
15	16	17	18	19
22	23	24	25	26
29	30	31		

JUN '17

M	T	W	T	F
			1	2
5	6	7	8	9
12	13	14	15	16
19	20	21	22	23
26	27	28	29	30

AUG	8, 9, 10	Teacher Duty Days - No School
	11	FIRST DAY OF CLASSES
	15, 22	Early Release Mondays
	29	Early Release Mondays
SEP	5	Labor Day - No School
	12, 19	Early Release Mondays
	20 - 23	Conferences - Min Day (Markham only)
	26	Early Release Mondays
OCT	3	Early Release Mondays
	7	End 1st Quarter (Markham)
	10, 17, 24	Early Release Mondays
	28	End of 1st Trimester (Sierra & Schnell)
	31	Early Release Mondays
NOV	1 - 4	Conferences - Min Day (Sierra and Schnell only)
	7	Early Release Mondays
	11	Veteran's Day - No School
	14	Early Release Mondays
	21 - 25	Fall Recess - No School
	28	Early Release Mondays
DEC	5, 12	Early Release Mondays
	16	End of 1st Semester (Markham) - Min Day District wide
	19 - 30	Winter Recess - No School
JAN	2	Winter Recess - No School
	9	Early Release Mondays
	16	Martin Luther King Jr. Day - No School
	23, 30	Early Release Mondays
FEB	6	Early Release Mondays
	13	Lincoln's Birthday - No School
	17	End of 2nd Trimester (Sierra & Schnell)
	20	President's Day - No School
	23, 24	Conferences - Min Day (District wide)
	27	Early Release Mondays
MAR	6	Early Release Mondays
	10	End of 3rd Quarter (Markham)
	13, 20	Early Release Mondays
	27	Early Release Mondays
APR	3	Early Release Mondays
	10 - 14	Spring Recess - No School
	17	Spring Recess - No School
	24	Early Release Mondays
MAY	1, 8	Early Release Mondays
	15, 22	Early Release Mondays
	26	LAST DAY OF CLASSES/ Min Day
	29	Memorial Day
JUN		HAVE A FUN SUMMER!

School Hours	Regular	Minimum Day	Early Release Mondays
	141	8	31
Markham School	7:50 - 2:19	7:50 - 11:31	7:50 - 1:05
Sierra School	8:45 - 2:55	8:45 - 12:25	8:45 - 1:45
Schnell School	9:00 - 3:10	9:00 - 12:45	9:00 - 1:55

First Day of Classes:	Thursday, August 11, 2016
Last Day of Classes:	Friday, May 26, 2017

[redacted]
Board approved 12-16-15

Sacramento City Unified School District

Human Resource Services

Traditional Attendance Calendar

2016 - 2017 School Year

JULY							
S	M	T	W	T	F	S	
					1	2	0
3	4	5	6	7	8	9	0
10	11	12	13	14	15	16	0
17	18	19	20	21	22	23	0
24	25	26	27	28	29	30	0
31							0
					Days:		0

AUGUST							
S	M	T	W	T	F	S	
	1	2	3	4	5	6	0
7	8	9	10	11	12	13	0
14	15	16	17	18	19	20	0
21	22	23	24	25	26	27	0
28	29	30	31				0
					Days:		0

SEPTEMBER							
S	M	T	W	T	F	S	
				*▪▪1	2	3	2
4	5	6	7	8	9	10	4
11	12	13	14	15	16	17	5
18	19	20	21	22	23	24	5
25	26	27	28	29	30		5
					Days:		21

OCTOBER							
S	M	T	W	T	F	S	
						1	0
2	3	4	5	6	7	8	5
9	10	11	12	13	14	15	5
16	17	18	19	20	21	22	5
23	24	25	26	27	28	29	5
30	31						1
					Days:		21

NOVEMBER							
S	M	T	W	T	F	S	
		1	2	3	4▪	5	4
6	▪7	8	9	10	11	12	4
13	14	15	16	17	18	19	5
20	21	22	23	24	25	26	0
27	28	29	30				3
					Days:		0

DECEMBER							
S	M	T	W	T	F	S	
				1	2•	3	2
4	•5	6	7	8	9	10	5
11	12	13	14	15	16	17	5
18	19	20	21	22	23	24	0
25	26	27	28	29	30	31	3
					Days:		0

JANUARY							
S	M	T	W	T	F	S	
							0
1	2	3	4	5	6	7	0
8	9	10	11	12	13	14	5
15	16	17	18	19	20	21	4
22	23	24	25	26	27*▪	28	5
29	*▪30	31					2
					Days:		16

FEBRUARY							
S	M	T	W	T	F	S	
			1	2	3	4	3
5	6	7	8	9	10	11	5
12	13	14	15	16	17	18	4
19	20	21	22	23	24	25	4
26	27	28					2
					Days:		0

MARCH							
S	M	T	W	T	F	S	
			1	2	3	4	3
5	6	7	8	9	10	11	5
12	13	14	15	16	17•	18	5
19	•20	21	22	23	24	25	6
26	27	28	29	30	31		5
					Days:		0

APRIL							
S	M	T	W	T	F	S	
						1	0
2	3	4	5	6	7•	8	5
9	10	11	12	13	14	15	0
16	▪17	18	19	20	21	22	5
23	24	25	26	27	28	29	5
30							0
					Days:		15

MAY							
S	M	T	W	T	F	S	
	1	2	3	4	5	6	5
7	8	9	10	11	12	13	5
14	15	16	17	18	19	20	5
21	22	23	24	25	26	27	5
28	29	30	31				2
					Days:		0

JUNE							
S	M	T	W	T	F	S	
				1	2	3	2
4	5	6	7	8	9	10	5
11	12	13	14	15*▪▪	[redacted]	17	4
18	19	20	21	22	23	24	0
25	26	27	28	29	30		0
					Days:		0

Legend: * Semester Begins and Ends ▪ Quarter Begins and Ends • Trimester Begins and Ends ☐ School Month Ends

Full and Shortened Days	180
Common Planning Time	3
Faculty Work Day	1
Total Service Days	184

RED School Holidays / Other Days Not in Session

PURPLE Non-Instructional Day/Faculty Work Day

Revised: 11-30-2015; 5-26-16
Board Approved: 12-10-15

EXHIBIT 12
Page 127

SAN DIEGO UNIFIED SCHOOL DISTRICT
2016-17 TRADITIONAL ACADEMIC CALENDAR
AUGUST 29 START DATE

Approved by the Board of Education: June 9, 2015

	M	T	W	Th	F	M	T	W	Th	F	M	T	W	Th	F	M	T	W	Th	F	M	T	W	Th	F
JULY					1	4 H	5	6	7	8	11	12	13	14	15	18	19	20	21	22	25	26	27	28	29
AUGUST	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	23	24	25	26	29 F	30	31		
SEPTEMBER				1	2	5 H	6	7	8	9	12	13	14	15	16	19	20	21	22	23	26	27	28	29	30
OCTOBER	3	4	5	6	7	10	11	12	13	14	17	18	19	20	21	24	25	26	27	28	31				
NOVEMBER		1	2	3	4	7	8	9	10	11 H	14	15	16	17	18	21 NI	22 NI	23 NI	24 H	25 H	28	29	30		
DECEMBER				1	2	5	6	7	8	9	12	13	14	15	16	19 NI	20 NI	21 NI	22 NI	23 H	26 H	27 NI	28 NI	29 NI	30 H
JANUARY	2 H	3	4	5	6	9	10	11	12	13	16 H	17	18	19	20	23	24	25	26	27	30	31			
FEBRUARY			1	2	3	6	7	8	9	10	13	14	15	16	17 H	20 H	21	22	23	24	27	28			
MARCH			1	2	3	6	7	8	9	10	13	14	15	16	17	20	21	22	23	24	27 NI	28 NI	29 NI	30 NI	31 NI
APRIL	3	4	5	6	7	10	11	12	13	14	17	18	19	20	21	24	25	26	27	28					
MAY	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	23	24	25	26 NI	29 H	30	31		
JUNE				1	2	5	6	7	8	9	12	13	14 L	15	16	19	20	21	22	23	26	27	28	29	30

	TOTALS
Jul	
Aug	3
Sep	21
Oct	21
Nov	16
Dec	12
Jan	20
Feb	18
Mar	18
Apr	20
May	21
Jun	10
Total	180

H	Holiday	**Blue**
F/L	First/Last Day of School	**Yellow**
N/I	Non-Instructional Day (No School)	**Green**
I	Instruction Day	**Yellow**

EXHIBIT 12

SAN RAFAEL CITY SCHOOLS 2016-2017 DISTRICT CALENDAR

REVISED 2/8/2016

Month	M	T	W	T	F		Calendar Details
August 2016	1	2	3	4	5	10	Aug. 15: K-8 Staff Development Aug. 16-17: K-8 Teacher Work Days Aug. 15 and 17: 9-12 Teacher Workdays Aug. 16: 9-12 Staff Development Aug. 18: First Day of School, PreK-12
	8	9	10	11	12		
	15	16	17	18	19		
	22	23	24	25	26		
	29	30	31				
September 2016				1	2	21	Sept. 5 : Labor Day Holiday
	5	6	7	8	9		
	12	13	14	15	16		
	19	20	21	22	23		
	26	27	28	29	30		
October 2016	3	4	5	6	7	20	Oct. 17-21: K-5 Conference Week Oct. 17: K-5 Teacher Work Day Oct. 17: 6-8 Staff Development Oct. 17: 9-12 Non stud/Non tchr day
	10	11	12	13	14		
	17	18	19	20	21		
	24	25	26	27	28		
	31						
November 2016		1	2	3	4	18	Nov. 11: Veteran's Day *Nov. 23 & 25: Local Recess Days* Nov. 24: Thanksgiving
	7	8	9	10	11		
	14	15	16	17	18		
	21	22	23	24	25		
	28	29	30				
December 2016				1	2	16	Dec.23 & 26: Christmas Eve & Christmas Day (Observed) Dec.30: New Year's Eve (Observed)
	5	6	7	8	9		
	12	13	14	15	16		
	19	20	21	22	23		
	26	27	28	29	30		
January 2017	2	3	4	5	6	15	Jan.2: New Year's Day (Observed) Jan. 9 K-5 Staff Development Jan 9. 6-12 Teacher Workday Jan.16: MLK Holiday
	9	10	11	12	13		
	16	17	18	19	20		
	23	24	25	26	27		
	30	31					
February 2017			1	2	3	15	Feb. 20-24 Mid-Winter Break
	6	7	8	9	10		
	13	14	15	16	17		
	20	21	22	23	24		
	27	28					
March 2017			1	2	3	22	March 20-24: K-5 Conference Week March 20: K-5 Tchr Work Day March 20: 6-8 Staff Development March 20: 9-12 Non stud/Non tchr day
	6	7	8	9	10		
	13	14	15	16	17		
	20	21	22	23	24		
	27	28	29	30	31		
April 2017	3	4	5	6	7	15	April 10-14: Spring Break
	10	11	12	13	14		
	17	18	19	20	21		
	24	25	26	27	28		
May 2017	1	2	3	4	5	22	May 29: Memorial Day
	8	9	10	11	12		
	15	16	17	18	19		
	22	23	24	25	26		
	29	30	31				
June 2017				1	2	6	June 8: Last Day of School June 9: K-5 Staff Development June 9: 6-12 Workday
	5	6	7	8	9		
	12	13	14	15	16		
	19	20	21	22	23		
	26	27	28	29	30		

First Day of School:
ALL STUDENTS
August 18, 2016

Teacher Work Days
K-8 Teachers: August 16 and 17, 2016
9-12 Teachers:August 15 and 17, 2016
K-5 Teachers: October 17, 2016
6-12 Teachers: January 9, 2017
K-5 Teachers: March 20, 2017
6-12 Teachers: June 9, 2017

Staff Development Days
K-8 Teachers:August 15, 2016
9-12 Teachers: August 16, 2016
6-8 Teachers. October 17, 2016
K-5 Teachers: January 9, 2017
6-8 Teachers: March 20, 2017
K-5 Teachers: June 9, 2017

Classified Staff Holidays
July 4
September 5
November 11
November 24 and 25
December 23. 26 and 30
January 2
January 16
February 20 and 24
April 14 (Friday of Spring Break)
May 29

Thanksgiving Break:
November 23 - 25, 2016

Winter Break:
December 23, 2016-January 9, 2017

Mid-Winter Break:
February 20-24, 2017

Spring Break:
April 10-14, 2017*

1st Semester ends
December 22, 2016

2nd Semester ends:
June 8, 2017

K-12 Last Day of School:
June 8, 2017
8th grade Promotions
High School Graduations

Student Days: 180 Total Staff Days: 184

Teacher Work Days: 4

Staff Development Days (K-8): 3 High School Staff Development Days: 1

Key:
Blue=Classified Staff Holiday
Green=Teacher Workday

* Revised Calendar reflects change in Spring Break dates from April 17-21, 2017 to April 10-14, 2017

Board Approved:
2/8/2016

SANTA BARBARA UNIFIED SCHOOL DISTRICT

720 Santa Barbara Street, Santa Barbara, CA 93101 (805) 963-4338

TRADITIONAL 2016-2017 CALENDAR

180 STUDENT DAYS

	2016	S	M	T	W	T	F	S
JULY	★4 Independence Day	3	★4	5	6	7	8	9
		10	11	12	13	14	15	16
		17	18	19	20	21	22	23
		24	25	26	27	28	29	30
		31						
AUG	✧ New Teachers Report		1	2	3	4	5	6
	➢ Professional Learning Days	7	8	9	10	11	12	13
	➔ All Staff on Duty	14	✧15	➢16	➢17	➢18	➔19	20
	⏏⏏ First Day of School	21	⏏⏏22	23	24	25	26	27
		28	29	30	31			
SEPT	★5 Labor Day Holiday					1	2	3
		4	★5	6	7	8	9	10
		11	12	13	14	15	16	17
		18	19	20	21	22	23	24
		25	26	27	28	29	30	
OCT								1
		2	3	4	5	6	7	8
	♦ End of Term 1 – SMHS (minimum day)	9	10	11	12	13	14	15
	# Minimum Day (Elem only)	16	17	18	19	20	♦21	22
	➢ Professional Learning Day (student free day)	23	24	25	26	27	#28	29
		30	➢31					
NOV	★11 Veterans' Day Holiday							
	⏏ End of Trimester Min. Day (Elem)			1	2	3	4	5
	▲ Parent Conferences (Elem)	6	7	8	9	⏏10	★11	12
	☆Recess Day	13	▲14	▲15	▲16	▲17	▲18	19
	★24 Thanksgiving Day	20	☆21	☆22	☆23	★24	● 25	26
	●25 Board Holiday	27	28	29	30			
DEC	☆ Winter Recess					1	2	3
	★25 Legal Holiday	4	5	6	7	8	9	10
	● Board Holiday	11	12	13	14	15	#16	17
	# Minimum Day (Elem only)	18	☆19	☆20	☆21	☆22	●23	24
		25	★26	☆27	☆28	☆29	●30	31

	S	M	T	W	T	F	S	2017
JAN	1	★2	3	4	5	6	7	★2 New Years Day Observed
	8	9	10	11	12	13	14	
	15	★16	17	18	19	⏏♦20	21	★16 Martin Luther King Day
	22	23	24	25	26	27	28	⏏♦ End of Sem/Term 2 (SMHS) Min. Day (Sec)
	29	30	31					
FEB				1	2	3	4	
	5	6	7	8	9	10	11	★17 Lincoln's Birthday Obs
	12	13	14	15	16	★17	18	★20 Presidents' Day
	19	★20	21	22	23	24	25	
	26	27	28					
MAR				1	2	3	4	⏏ End 2nd Trimester Min. Day (Elem)
	5	6	7	8	9	⏏10	11	▲ Parent Conferences (Elem)
	12	▲13	▲14	▲15	▲16	▲17	18	♦ End of Term 3 – SMHS (minimum day)
	19	20	21	22	23	♦24	25	☆Recess Day
	26	☆27	☆28	☆29	☆30	●31		● Board Holiday
APR							1	
	2	➢3	4	5	6	7	8	➢Professional Learning Day (student free day)
	9	10	11	12	13	14	15	
	16	17	18	19	20	21	22	
	23	24	25	26	27	28	29	
	30							
MAY								
		1	2	3	4	5	6	
	7	8	9	10	11	12	13	
	14	15	16	17	18	19	20	
	21	22	23	24	25	26	27	★29 Memorial Day Holiday
	28	★29	30	31				
JUNE					1	2	3	⏏⏏ School's Out Min. Day
	4	5	6	7	⏏⏏8	➔9	10	➔ Last Day for All Staff
	11	12	13	14	15	16	17	
	18	19	20	21	22	23	24	
	25	26	27	28	29	30		

TEACHING CONTRACT YEAR:

New Teachers	188 Days
Returning Teachers	187 Days
Students	180 Days

➔ All Staff Days Only (2 days)
➢ Professional Learning Days (5 days)
★ Legal Holidays (10 days)
Minimum Days (2 days- Elementary Only)

● Board Holidays (4 days)
☆ Recess Days (14 days)
✧ Report Date – New Teachers
♦ End of Term – Minimum Day

▲ Parent Conferences-Min. Day Elem only
⏏ End of Trimesters – Minimum Day
⏏⏏ First Day/Last Day of School
Board approved 4.26.16

DISTRICT OFFICE IS CLOSED ALL LEGAL AND BOARD HOLIDAYS

EXHIBIT D

KEY **Bold – Non-School Days**
* – Minimum Days

VISTA UNIFIED SCHOOL DISTRICT
2016-2017 School Calendar

Board Approved: 12/12/13
Board Approved Revision: 1/21/16

School Month	M	T	W	T	F	Student Days	Teacher Days	Key Dates	Explanations
July					1				
	4	5	6	7	8			July **4**	Independence Day *(Legal Holiday)*
	11	12	13	14	15				
	18	19	20	21	22				
	25	26	27	28	29				
August	1	2	3	4	5				
	8	9	10	11	12			Aug. 15	District Professional Development Day (Non-Student Day)
	15	*16*	17	18	19			Aug. 16	Site Professional Development Day (Non-Student Day)
	22	23	24	25	26			***Aug. 17***	***First Day of School***
	29	30	31			11	13		
September				1	2				
	5	6	7*	8	9			Sept. **5**	Labor Day Holiday *(Legal Holiday)*
	12	13	14	15	16			Sept. 7	TK-8 Professional Development Day (Minimum Day)
	19	20	21	22	23				
	26	27	28	29	30	21	21		
October	3	4	5	6*	7*				
	10	11	12	13	14			Oct. 6-7	MVHS Finals – (Minimum Days)
	17	18	19	20	21				
	24	25	26	27	28				
	31					21	21		
November		1	2	3	4				
	7*	8*	9*	10*	**11**			Nov. **11**	Veterans' Day Holiday *(Legal Holiday)*
	14	15	16	17	18			Nov. 7-10	TK-5 Parent Teacher Conferences (Minimum Day)
	21	**22**	**23**	**24**	**25**			Nov. 8 & 10	6-8 Parent Teacher Conferences (Minimum Day)
	28	29	30			16	16	Nov. 21-25	TK-12 Non-Student Days
								Nov. **24**	Thanksgiving Holiday *(Legal Holiday)*
December				1	2				
	5	6	7	8	9			Dec. 15-16	MVHS Finals
	12	13	14*	15*	16*			Dec. 14-16	RBVHS & VHS Finals
	19	**20**	**21**	**22**	**23**			Dec. **19-30**	Winter Recess (School Resumes Jan. 4)
	26	**27**	**28**	**29**	**30**	12	12	Dec. **23**	Observed Christmas Eve (Legal Holiday)
								Dec. **26**	Observed Christmas Day *(Legal Holiday)*
January	**2**	**3***	4	5	6				
	9	10	**11**	12	**13**			Jan. **2**	Observed New Year's Day *(Legal Holiday)*
	16	17	18	19	20			Jan. **3***	HS Professional Development Day (Non Student Day)
	23	24	25	26	27			Jan. **3***	TK-8 Non Student Day/Non Staff Day
	30	31				18	20	Jan **13**	District Professional Development Day (Non-Student Day)
								Jan. **16**	M.L. King Birthday *(Legal Holiday)*
February			1	2	3				
	6	7	8*	9	**10**			Feb. 8	TK-8 Professional Development Day (Minimum Day)
	13	14	15	16	**17**			Feb. **17**	Lincoln's Birthday *(Observed Holiday)*
	20	**21**	22	23	24			Feb. **20**	President's Day *(Legal Holiday)*
	27	28				18	18		
March			1	2	3				
	6	7	8	9	10			Mar. 14 & 16	6-8 Parent Teacher Conferences (Minimum Day)
	13	14*	15	16*	17*			Mar. 16-17	MVHS Finals (Minimum Days)
	20	21	22	23	24			Mar. **27-31**	Spring Break
	27	**28**	**29**	**30**	**31**	18	18		
April	3	4	5	6	7				
	10	11	12	13	14			Apr. 16	Easter
	17	18	19	20	21				
	24	25	26	27	28	20	20		
May	1	2	3	4	5				
	8	9	**10**	**11**	12				
	15	16	17	18	19				
	22	23	24	25	26	22	22	May **29**	Memorial Day Holiday *(Legal Holiday)*
	29	30	31						
June				1	2				
	5*	6*	⚠	8	9			June 5*-7*	RBVHS & VHS Finals (Minimum Days)
	12	13	14	15	16			June 6* & 7*	MVHS Finals (Minimum Days)
	19	20	21	22	23			***June 7***	***Last Day of School***
	26	27	28	29	30	5	5		

182 STUDENT DAYS

PERSONAL BELIEFS EXEMPTION TO REQUIRED IMMUNIZATIONS

CDPH

STUDENT NAME (LAST, FIRST, MIDDLE)	GENDER ☐ M ☐ F	BIRTHDATE MONTH DAY YEAR __ __ / __ __ / __ __ __ __	TELEPHONE NUMBER
PARENT/GUARDIAN – NAME		ADDRESS	

A. AUTHORIZED HEALTH CARE PRACTITIONER LICENSED IN CALIFORNIA – FILL OUT THIS SECTION

I am a (check one): ☐ M.D./D.O. ☐ Nurse Practitioner ☐ Physician Assistant ☐ Naturopathic Doctor ☐ Credentialed School Nurse

Provision of Information: I have provided the parent or guardian of the student named above, the adult who has assumed responsibility for the care and custody of the student, or the student if an emancipated minor, with information regarding 1) the benefits and risks of immunization and 2) the health risks to the student and to the community of the communicable diseases for which immunization is required in California (immunizations listed in Table below).

Signature of authorized health care practitioner

Date - within 6 months before entry to child care or school

Practitioner name, address, telephone number:

B. PARENT OR GUARDIAN – FILL OUT THESE SECTIONS

I. Check one of the boxes below:

☐ **Receipt of Information:** I have received information provided by an authorized health care practitioner regarding 1) the benefits and risks of immunization and 2) the health risks to the student named above and to the community of the communicable diseases for which immunization is required in California (immunizations listed in Table below).

☐ **Religious beliefs:** I am a member of a religion which prohibits me from seeking medical advice or treatment from authorized health care practitioners. (Signature of a health care practitioner not required in Part A.)

Signature of parent or guardian

Date - within 6 months before entry to child care or school

II. AFFIDAVIT

Immunizations already received: I have provided the child care or school with a record of all immunizations the student has received that are required for admission (California Health and Safety Code §120365).

Immunizations for which exemption is requested: An unimmunized student and the student's contacts at school and home are at greater risk of becoming ill with a vaccine-preventable disease. I understand that an unimmunized student may be excluded from attending school or child care during an outbreak of, or after exposure to, any of these diseases for the protection of the student and others (17 CCR §6060). I hereby request exemption of the student named above from the required immunizations checked below because such immunization is contrary to my beliefs.

School Category	Table of Required Immunizations – Check box(es) to request exemption.
Child Care Only	☐ ***Haemophilus influenzae* type b** (Hib meningitis)
Child Care and K-12th Grade	☐ **DTaP** (Diphtheria, Tetanus, Pertussis [whooping cough]) ☐ **Hepatitis B** ☐ **MMR** (Measles, Mumps, Rubella) ☐ **Polio** ☐ **Varicella** (Chickenpox)
7th Grade Advancement (or admission at 7-12th Grade)	☐ **Tdap** (Tetanus, reduced Diphtheria, Pertussis [whooping cough])

Signature of parent or guardian

Date

The California Department of Public Health places strict controls on the gathering and use of personally identifiable data. Personal information is not disclosed, made available, or otherwise used for purposes other than those specified at the time of collection, except with consent or as authorized by law or regulation. The Department's information management practices are consistent with the Information Practices Act (Civil Code Section 1798 et seq.), the Public Records Act (Government Code Section 6250 et seq.), Government Code Sections 11015.5 and 11019.9, and with other applicable laws pertaining to information privacy.