In vertebrates, genes of the major histocompatibility complex (MHC), with their pronounced polymorphism, potentially represent outstanding examples for the selective advantages of genetic diversity (1). Theoretical models predicted that, within an individual, MHC alleles can be subjected to two opposing selective forces, resulting in an optimal number of genes at intermediate individual MHC diversity (2, 3). Diversifying selection increases heterozygosity and enables wider recognition of pathogens (4). This process is opposed by the need to delete T cells that react with self-peptide–MHC combinations (5) from the repertoire, which has been proposed as a possible mechanism constraining expansion of MHC genes. Because too high MHC diversity might delimit T cell diversity, it might also impose limitations on the efficiency of pathogen recognition. However, empirical evidence demonstrating fitness benefits in terms of parasite resistance caused by this type of optimal MHC diversity has been lacking. Therefore, we tested whether three-spined sticklebacks (Gasterosteus aculeatus L.) carrying an intermediate level of individual MHC diversity also displayed the strongest level of resistance against parasite infection. Sticklebacks are particularly suited to test MHC optimality, because MHC class II genotypes can differ markedly in resistance against several infectious agents (2).

Infection decreased host body condition, which is a fitness-relevant trait in sticklebacks (10). Thus, intensity of infection correlated negatively to the change in body condition of the fish during the experiment [repeated measures analysis of variance (ANOVA), including control and singly infected fish: total number of parasites * time, F(1,141) = 4.351, P = 0.039]. Therefore, we have provided experimental evidence that multiple parasites can select for optimal rather than maximal MHC diversity and that intermediate rather than maximal genetic diversity confers the highest level of fitness.

References and Notes
9. Materials and Methods are available as supporting online material on Science Online.

Supporting Online Material
www.sciencemag.org/cgi/content/full/301/5638/1343/DC1
Materials and Methods
References
Table S1
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Parasite Selection for Immunogenetic Optimality
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Fig. 1. (A) Parasite species used to infect three-spined stickleback (G. aculeatus L.). (B) Relation between number of expressed MHC class IIB molecules and mean parasite load [expressed as summed residuals from General Linear Model analysis, models included exposure dose as covariate and sibship as random factor (9)] for double-exposed fish. The function matches a quadratic polynomial [r² = 0.79, ANOVA F(2,4) = 7.38, P = 0.045] with a minimum of 5.82 alleles only when considering the combined effect from all three species [fit of polynomials for residuals from single parasite analysis: A. crassus, r² = 0.96, F(2,4) = 0.12, P = 0.886; C. lacustris, r² = 0.48, F(2,4) = 1.86, P = 0.268; D. spathaceum, r² = 0.01, F(2,4) = 0.80, P = 0.991]. The dotted line shows the mean from all residuals. Error bars show ±5E, controlled for sibship effects and exposure dose. (C) Relation of mean number of expressed MHC class IIB molecules per sibship and the mean of the slopes between parasite loads (controlled for exposure dose) associated with the four MHC class IIB genotypes of the corresponding sibship (9). The linear relation [f(x) = -0.265 + 0.053x, r² = 0.79, F(1,4) = 15.04, P = 0.013] has a zero intercept at 4.96 alleles, which can be equated with the immunogenetic optimum. Dashed lines show 95% confidence interval.