TBE per year. Up to 30% of adults infected by the zoonotic arbovirus develop meningitis or meningoencephalitis and the lethality of TBE in Europe is up to 1%. The implementation of TBE vaccination with inactivated whole virus vaccines led to a dramatic decline of clinical cases. However, immunological responsiveness to TBE booster vaccination is dependent on the time of the last vaccination as well as age. Three to four years after TBE vaccination, 30% of people aged 60 years or older did not have protective TBE antibody levels, whereas 99% of people below the age of 40 were protected by the TBE vaccine (Fig. 2) (13). This emphasizes the need to follow regular booster vaccinations in old age to maintain protective antibody levels.

HOW DOES IMMUNOSENESCENCE INFLUENCE VACCINE EFFICACY?

The aging process affects a wide range of cell types, including hematopoietic stem cells (HSCs), lymphoid progenitors, thymic epithelial cells, mature lymphocytes, as well as cells of the innate immune system. These age-related changes contribute to the decreased vaccine efficacy observed in the elderly in several ways. HSCs reside in the bone marrow, can give rise to all blood cell types including the myeloid and lymphoid lineages, and are long lived due to an extensive self-renewal capacity. However, studies on humans and animals indicate that HSCs show signs of aging. HSCs from elderly persons have a reduced capacity to differentiate into the lymphoid lineage, an increased expression of the cell-cycle inhibitor $p16^{INK4A}$, and a decreased homing and reconstitution potential (14,15) (Fig. 3). Apart from these intrinsic defects, the age-related decline in hematopoietic tissue and an altered hematopoietic microenvironment may further contribute to defects in T and B cell progenitor cells and to a decline in lymphopoiesis during aging. The most prominent event during aging, however, is the continuous loss of thymic epithelial space beginning at the age of one year and resulting in a dramatic decline in thymopoiesis in old age (Fig. 4). The thymus, the central lymphoid organ, is responsible for the maturation and selection of antigen-inexperienced, naive T cells that regenerate the peripheral T-cell pool and retain the capability of the adaptive immune system to respond to a variety of different pathogens. Age-related changes in bone marrow stromal cells have also been shown to affect B-cell development, characterized by lower numbers of pre–B cells and fewer mature B cells that leave the bone marrow.

T Lymphocytes

Despite the age-related decrease in thymopoiesis and the continuous exposure of the immune system to replicative stress through recurrent infections, the size of the peripheral T-cell pool remains stable throughout life. However, the composition of the peripheral T-cell pool changes during aging, with a dramatic decline in naive T-cell numbers and a concomitant increase of antigen-experienced T cells (Fig. 5). Although already low in numbers, peripheral naive T cells exhibit functional deficits in old age. These functional deficits comprise shortened telomeres, a restricted T-cell receptor (TCR) repertoire, impaired TCR-signaling, low interleukin (IL)-2 production, and an impaired generation of functional memory T cells (17). The functional impairments of peripheral naive T cells in

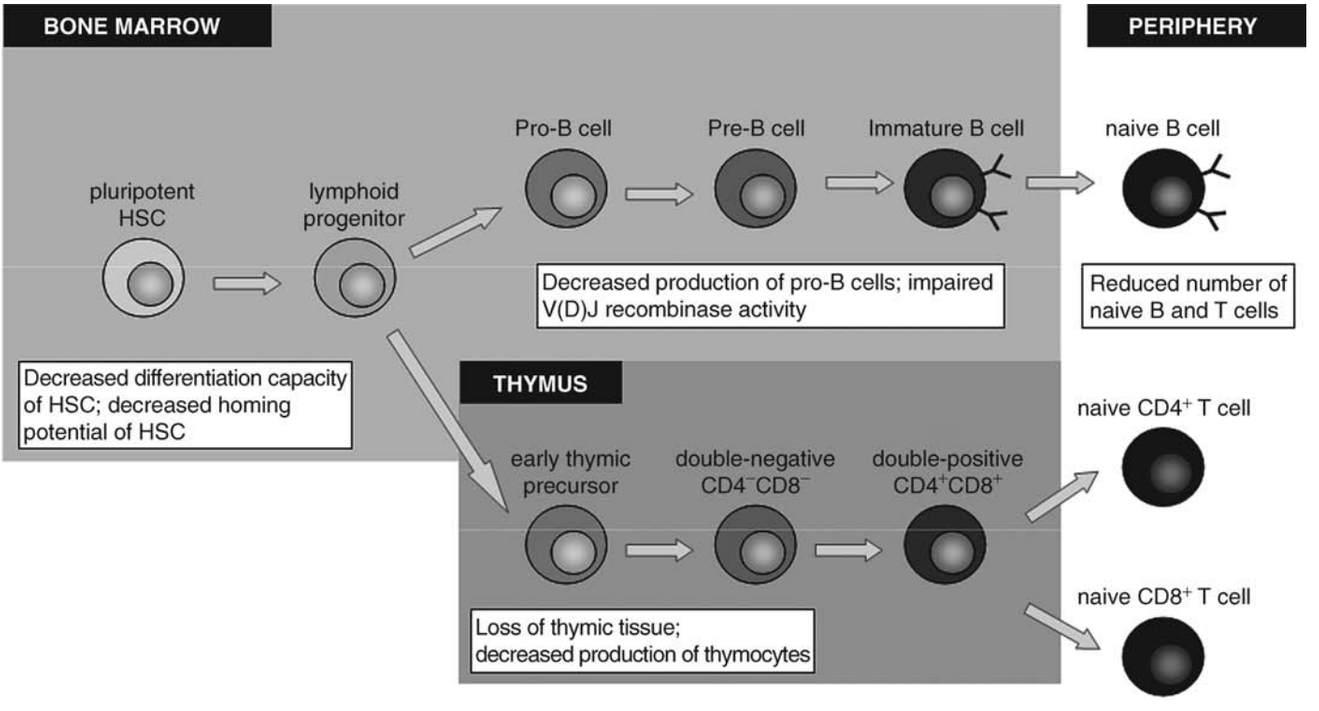

Figure 3 Age-associated alterations in lymphopoiesis. Pluripotent stem cells from the bone marrow give rise to lymphoid progenitors that differentiate into mature B and T lymphocytes in the bone marrow and the thymus, respectively. The most relevant age-related defects in T and B cell development are highlighted. See text for details.